CLINICAL REVIEW

PLA #96-1433

NEUMEGA® OPRELVEKIN (RHIL-11)

FOR THE

PREVENTION

OF

CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA

FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

BLA #96-1433
NEUMEGA® OPRELVEKIN (RHIL-11)

1. INTRODUCTION

GENERAL

INTERLEUKIN ELEVEN (IL-11) IS A PLEIOTROPIC CYTOKINE PRODUCED IN BONE MARROW STROMAL CELLS. IT IS A MEMBER OF A SUPER-FAMILY OF HUMAN GROWTH FACTORS WHICH INCLUDES HUMAN GROWTH HORMONE, GRANULOCYTE COLONY-STIMULATING FACTOR (G-CSF), AND INTERLEUKIN SIX. AMONG THE ACTIVITIES OF RHIL-11 ARE THE [1] STIMULATION OF PROLIFERATION OF HEMATOPOIETIC STEM CELLS AND MEGAKARYOCYTE PROGENITOR CELLS AND [2] THE INDUCTION OF MEGAKARYOCME MATURATION. *IN VITRO* STUDIES HAVE SHOWN SYNERGISM WITH INTERLEUKIN THREE, STEM CELL FACTOR, AND FLT3 LIGAND. ANIMAL STUDIES SHOWED THAT THE PREDOMINANT HEMATOPOIETIC ACTIVITY OF RHIL-11 WAS THE STIMULATION OF MEGAKARYOCYTOPOIESIS, WI-I-H A RESULTANT INCREASE IN PERIPHERAL PLATELET COUNTS. ANEMIA WAS OBSERVED IN ALL SPECIES STUDIED. RHIL-11 ALSO INDUCED ACUTE-PHASE PROTEINS AND ACTIVATED OSTEOCLASTS TO STIMULATE THE RELEASE OF CA++. RHIL-11 HAS BEEN ASSIGNED THE DESIGNATED NAME OPRELVEKIN BY USAN. NEUMEGA® IS GENETIC INSTITUTE'S TRADE NAME FOR OPRELVEKIN. THE CHRONOLOGY LEADING TO THE SUBMISSION OF THIS BIOLOGIC LICENSE APPLICATION (BLA) IS SUMMARIZED BELOW.

TABLE Nº 1 - CHRONOLOGY FOR BLA #96-1433

DATE	ACTIVITY
AUGUST 1992	PRE-IND MEETING
SEPTEMBER 1992	BB-IND 4751 SUBMITTED
NOVEMBER 1992	CLINICAL TRIALS INITIATED
AUGUST 1995	END-OF-PHASE 2 MEETING
AUGUST 1996	PRE-BLA MEETING
DECEMBER 1996	BLA 96-1433 SUBMITTED

PROPOSED INDICATION

"NEUMEGA® IS INDICATED FOR THE PREVENTION OF CHEMOTHERAPY-INDUCED THROMBOCYTOPENIA AND THE REDUCTION OF THE NEED FOR PLATELET TRANSFUSIONS IN PATIENTS WITH NON-MYELOID MALIGNANCIES."

CLINICAL DEVELOPMENT PROGRAM

THE CLINICAL DEVELOPMENT PLAN FOR NEUMEGA® HAS BEEN WELL PLANNED AND OF HIGH QUALITY. TO DATE, OVER 300 PATIENTS AND 72 NORMAL VOLUNTEERS HAVE RECEIVED NEUMEGA®. MOST OF THE TRIALS HAVE BEEN RANDOMIZED AND PLACEBO-CONTROLLED. PHASE I STUDIES HAVE BEEN CONDUCTED IN BOTH ADULT PATIENTS RECEIVING MYELOSUPPRESSIVE CHEMOTHERAPY AND ALSO IN ADULT PATIENTS RECEIVING MYELOABLATIVE CHEMOTHERAPY. A PHASE I TRIAL IN PEDIATRIC PATIENTS

receiving myelosuppressive chemotherapy is nearing completion, and a phase I/2 trial of Neumega® following peripheral blood progenitor cell transplantation has just been initiated. Randomized, double-blind, placebo-controlled phase 2 trials have been completed in three different clinical settings: [1] for the primary prophylaxis of severe chemotherapy-induced thrombocytopenia (CIT) following myelosuppressive chemotherapy; [2] for the secondary prophylaxis of CIT in patients who had experienced severe CIT in a previous chemotherapy cycle; and [3] to accelerate marrow engraftment following autologous bone marrow transplantation (AuBMT). A randomized, double-blind, placebo-controlled phase 3 trial of Neumega® for the secondary prophylaxis of severe CIT is currently ongoing, as is an accompanying open-label extension. In addition, two trials in normal subjects have studied the effect of Neumega® on blood volume, Na^+ balance, and hemoglobin concentration. The clinical development program is summarized below.

TABLE Nº 2—Summary of the Clinical Trials with Neumega®

Study Nº	Study Characteristics			Description of Study
	N	Randomized	Double-Blinded	
C9206	16	No	No	Initial Phase 1 Trial (Patients with Breast Cancer)
C9301	21	No	No	Phase 1/2 Trial after AuBMT for Breast Cancer
C9305	23	No	No	Ongoing Phase 1/2 Trial in Pediatric Patients
C9308	93	Yes	Yes	Phase 2 Trial in Patients with Prior Severe CIT
C9313	80	Yes	Yes	Phase 2 Trial after AuBMT for Breast Cancer
C9314	12	Yes	Yes	Blood Volume & Na^+ Balance in Normal Volunteers
C9406	24	Yes	No	PK Study of IV *vs* SQ IL-11 in Normal Volunteers
C9413	24	Yes	No	Bioequivalence of Two Formulations (Volunteers)
C9416	77	Yes	Yes	Phase 2 Trial for Prevention of Severe CIT
C9504	Ongoing	Yes	Yes	Ongoing Phase 3 Trial in Patients with Prior CIT
C9515	18	Yes	Yes	Effect of Diuretic on Anemia in Normal Volunteers
C9525	Ongoing	Yes	Yes	Phase 1/2 Trial following PBPC Transplantation
C9528	Ongoing	N/A	N/A	Ongoing, Open-Label Follow-up to Study C9504

Pivotal Trials to Support Licensure

As noted, three randomized, double-blind, placebo-controlled trials were conducted as part of the phase 2 clinical development program. The initial purpose of these studies was to obtain an accurate estimate of the magnitude of the treatment effect, and also to serve as prototypes for the design of the phase 3 trials. However, in the two studies in which Neumega® was administered following myelosuppressive chemotherapy (C9308 and C9416) analysis revealed a decrease in the number of patients receiving platelet

transfusion when compared to placebo. After consultation with the FDA, it was decided to submit the results of these two studies to support the licensure of Neumega® for "*...the prevention of chemotherapy-induced thrombocytopenia and the reduction of the need for platelet transfusions*...." These two studies are briefly summarized below.

- ☒ Study C9308 was a study of two doses of Neumega® in patients who had an episode of severe thrombocytopenia (platelet count $<20{,}000/\mu L$) and had received at least one platelet transfusion in the preceding cycle. The patients received the same chemotherapy as in the previous cycle without dose reduction. The primary endpoint was the number of patients not requiring platelet transfusion in the subsequent cycle.[A]

- ☒ Study C9416 was a study using the higher dose of Neumega® from study C9308 as prophylaxis for severe thrombocytopenia. There were two blinded cycles, with no crossover. Four additional open-label cycles were allowed. The primary endpoint was whether or not platelet transfusions were required.

The use of Neumega® to accelerate engraftment following bone marrow transplantation is not being considered as part of this application.

II. PHASE 1 TRIALS IN THE POST-MYELOSUPPRESSIVE CHEMOTHERAPY SETTING

Study C9206—Phase 1 Trial in Adult Patients

Study C9206 "*Phase 1 study of rhIL-11 alone and following dose-intense chemotherapy in patients with stage 3B or 4 breast cancer*" was the initial phase 1 study of Neumega®. It was an open-label, non-randomized, dose-escalation study of doses of 10, 25, 50, 75, and 100 µg/kg/d in female patients with stage 3B or stage 4 breast cancer. Standard dose-escalation criteria were used. Patients received a 14-day course of Neumega® alone as a subcutaneous injection ("Cycle 0"), followed by a 14-day observation period. Patients then received up to four cycles of cyclophosphamide (CPA) and doxorubicin (DOX),[B] followed by the assigned dose of Neumega® on days 3 to 14, every 28 days. Concomitant myeloid growth factors were not given initially. The objective was the determination of the dose-limiting toxicity (DLT) and/or the maximum-tolerated dose (MTD) of Neumega®. The trial opened in November 1992 and closed in January 1994.

A total of 16 patients were studied. Initially, cohorts of three patients were studied at doses of 10, 25, 50, and 75 µg/kg/d. One patient received 100 µg/kg/d. Doses of ≤50 µg/kg/d were well-tolerated. Adverse events reported consisted primarily of asthenia, edema, nausea, rhinitis, headache, and injection site reactions. All three patients who received 75 µg/kg/d had at least one grade 2 toxicity, and two of the three discontinued participation in the study because of adverse events (myalgia, arthralgia, asthenia, and edema in one: portacatheter thrombosis in the other). Dose escalation was halted when

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[A] Based on this study, the phase 3 randomized, double-blind, placebo-controlled trial (C9504) in patients who had prior severe thrombocytopenia was initiated. This study is ongoing, and remains blinded.

[B] CPA 1500 mg/m^2 IV and DOX 60 mg/m^2 IV on day 1.

THE PATIENT WHO RECEIVED 100 μG/KG/D EXPERIENCED A THROMBOTIC CEREBROVASCULAR ACCIDENT (CVA). ALTHOUGH THE DEFINITION OF DLT HAD NOT BEEN MET, IT WAS CONCLUDED THAT 50 μG/KG/D WAS PROBABLY THE MTD, AND THREE ADDITIONAL PATIENTS WERE STUDIED AT THE 50 μG/KG/D DOSE.[c]

THIRTEEN PATIENTS RECEIVED NEUMEGA® BEFORE STARTING CHEMOTHERAPY IN CYCLE 0. ADVERSE EVENTS GENERALLY WERE JUDGED MILD TO MODERATE. THEY WERE WELL TOLERATED AND REVERSIBLE UPON COMPLETION OR DISCONTINUATION. ASTHENIA WAS REPORTED IN 11 PATIENTS (85%), AS WAS FEVER. NONE OF THE EPISODES OF FEVER WAS CONSIDERED CLINICALLY SIGNIFICANT, AND NONE REQUIRED INTERVENTION. THE FEVER DID NOT RECUR AFTER EACH DOSE. ALL FEVERS IN CYCLE 0 WERE GRADE 1 (<38° C). PERIPHERAL EDEMA OCCURRED IN TEN PATIENTS (77%). THE EDEMA WAS PRIMARILY DEPENDENT, REVERSIBLE, AND NOT DOSE-RELATED. LOCAL INJECTION SITE REACTIONS OCCURRED IN NINE PATIENTS (69%). THE REACTIONS WERE ERYTHEMATOUS, MACULAR, OCCASIONALLY INDURATED, AND SOMETIMES DELAYED IN APPEARANCE UNTIL SEVERAL DAYS AFTER DOSING. THE REACTIONS DID NOT RECUR AFTER EVERY INJECTION. RHINITIS, DESCRIBED AS NASAL CONGESTION, OCCURRED IN EIGHT PATIENTS (62%). TWO PATIENTS HAD CORRESPONDING HEADACHE. HEADACHE AND SINUS CONGESTION OCCURRED IN SIX PATIENTS (46%). MYALGIAS WERE ALSO REPORTED IN SIX PATIENTS. SEVERAL PATIENTS HAD RESPIRATORY COMPLAINTS, INCLUDING AN INCREASE IN COUGH (FOUR PATIENTS), AN INCREASE IN PLEURAL EFFUSION (THREE PATIENTS), OR DYSPNEA (TWO PATIENTS). ABDOMINAL PAIN, INCLUDING ABDOMINAL CRAMPING OR UPPER GASTROINTESTINAL DISCOMFORT, WAS REPORTED IN THREE PATIENTS (23%). PALPITATIONS AND TACHYCARDIA OCCURRED AT THE 50 AND 75 μG/KG/D DOSES. DIZZINESS OCCURRED IN THREE PATIENTS (ONE EACH IN THE 50, 75, AND 100 μG/KG/D DOSE GROUPS). MILD, TRANSIENT SYSTOLIC HYPOTENSION OCCURRED IN TWO PATIENTS, BUT DID NOT REQUIRE TREATMENT. VASODILATION, WHICH WAS DESCRIBED AS TRANSIENT EPISODES OF FLUSHING, OCCURRED IN THREE PATIENTS. NO TREATMENT WAS REQUIRED. VISUAL DISTURBANCES (AMBLYOPIA, BLINDING SPOTS) WERE REPORTED IN TWO PATIENTS. THERE WAS NO EVIDENCE OF A HYPERSENSITIVITY REACTION TO NEUMEGA®. RASH WAS REPORTED IN TWO PATIENTS. EACH ALSO HAD ERYTHEMA AT THE INJECTION SITES. TWO OTHER PATIENTS HAD TRANSIENT PRURITUS THAT DID NOT REQUIRE TREATMENT. NO GRADE 4 TOXICITIES WERE REPORTED. THREE ADVERSE EVENTS WERE GRADE 3 IN SEVERITY: TWO AT THE 10 μG/KG/D DOSE AND ONE AT THE 100 μG/KG/D DOSE.

THE MOST FREQUENTLY REPORTED LABORATORY ABNORMALITY WAS ANEMIA, WHICH DEVELOPED IN ALL 12 PATIENTS WHO COMPLETED CYCLE 0. THE ANEMIA DID NOT APPEAR TO BE DOSE-RELATED. THE DECREASE IN HEMOGLOBIN CONCENTRATION RANGED FROM A MEAN OF 15 TO 19% BELOW BASELINE. IT BEGAN WITHIN A FEW DAYS OF THE INITIATION OF NEUMEGA® ADMINISTRATION, AND REACHED A NADIR DURING THE SECOND WEEK OF DOSING. THE ANEMIA THEN IMPROVED OVER THE 2 WEEKS AFTER DISCONTINUATION OF NEUMEGA®. THE DECREASE IN HEMOGLOBIN WAS NOT DUE TO HEMOLYSIS OR BLEEDING. DIRECT MEASUREMENT OF PLASMA VOLUME AND RED BLOOD CELL MASS IN THREE PATIENTS SUGGESTED THAT THE DECREASE IN HEMOGLOBIN WAS PREDOMINANTLY RELATED TO AN INCREASE IN PLASMA VOLUME. NO PATIENT REQUIRED RED BLOOD CELL TRANSFUSION DURING CYCLE 0. SEVERAL OF THE PATIENTS WERE NOTED TO HAVE TRANSIENT, MILD ELEVATIONS OF AST, ALT, AND/OR ALKALINE PHOSPHATASE. MOST DID NOT EXPERIENCE ANY CHANGES IN THESE ENZYMES DURING SUBSEQUENT CYCLES. TWO PATIENTS HAD MILD HYPOCALCEMIA. OTHER SIGNIFICANT LABORATORY ABNORMALITIES WERE REPORTED INFREQUENTLY.

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[c] THE THREE ADDITIONAL PATIENTS ENROLLED AT THE 50 μG/KG/D DOSE DID NOT HAVE A CYCLE 0. INSTEAD, THEY RECEIVED THEIR FIRST DOSE OF NEUMEGA® AFTER THEIR FIRST CHEMOTHERAPY CYCLE (CYCLE 1).

Treatment with Neumega® in Cycle 0 was associated with an increase in platelet count during the second week of the cycle. The increase appeared to be dose-related. These data are summarized below.

TABLE Nº 3—Study C9206: Mean Platelet Count in Cycle 0

Dose Schedule	Number of Patients	Mean Platelet Count x 10^6/μL		Increase over Baseline
		Baseline	Maximum	
10 μg/kg/d x 14	3	230	400	74%
25 μg/kg/d x 14	3	318	590	86%
50 μg/kg/d x 14	3	234	478	104%
75 μg/kg/d x 14	3	247	688	179%

The patients received a total of 42 cycles of chemotherapy and Neumega®. The adverse events reported were similar to those reported during Cycle 0. The most commonly reported adverse events (reported by over half of the patients) were asthenia, fever, edema, pain, headache, neutropenic fever, hypotension, nausea and vomiting, myalgia, insomnia, increased cough, rhinitis, and alopecia. Patients experiencing prolonged severe neutropenia or neutropenic fever during Cycle 1 or 2 were allowed to receive a standard regimen of G-CSF in Cycles 3 and 4. Seven patients subsequently received a total of nine cycles of chemotherapy during which they did receive G-CSF. Concomitant use of G-CSF with Neumega® was not associated with any unexpected adverse events.

Platelet nadirs occurred on Days 10-12 during all four chemotherapy cycles. Platelet counts then rose and peaked at approximately Day 19, with mean values higher than baseline. Overall, mean platelet nadirs tended to worsen with subsequent cycles of chemotherapy. Twelve patients completed at least two 12-day cycles of Neumega® at their assigned doses after chemotherapy. Patients receiving <25 μg/kg/d appeared to have lower platelet count nadirs post-chemotherapy than those receiving ≥ 25 μg/kg/d, suggesting a dose effect. These data are summarized below.

TABLE Nº 4—Platelet Counts after Chemotherapy (Cycles 1 and 2)

Neumega® Dose	Mean Platelet Count x 10^6/μL					
	Cycle 1			Cycle 2		
	N	Baseline	Nadir	N	Baseline	Nadir
10 μg/kg/d	3	237	67	2	303	44
25 μg/kg/d	3	334	159	3	331	140
50 μg/kg/d	6	274	152	5	263	126
75 μg/kg/d	3	313	161	2	389	102

To assess whether Neumega® altered platelet aggregation in response to known platelet agonists, blood samples were drawn for standard platelet aggregometry testing on Day 1 before study drug dosing and on Day 15 during Cycle 1. Platelet aggregation was measured in response to a standard panel of agonists (collagen, epinephrine, ristocetin, arachidonic acid, and two concentrations of adenosine diphosphate [ADP]). No consistent or dose-related effect of Neumega® on platelet aggregation was observed. Most patients' samples showed decreased aggregation to the lower concentration of ADP on Day 1 and no increase in response on Day 15. Aggregation in response to the high dose of ADP and to ristocetin was normal for most patients both on Day 1 and on Day 15. Responses to collagen, epinephrine, and arachidonic acid were variable both on Day 1 and on Day 15, with no evidence of a treatment-related change either from normal to abnormal or from abnormal to normal responses.

Six patients withdrew from the study because of adverse reactions—four of which were judged to be "possibly" related to Neumega®. The patients who did not complete study C9206 because of adverse events are listed below.

TABLE Nº 5—Study C9206: Patient Discontinuations Due to Adverse Events

Patient Nº	Dose (µg/kg/d)	Cycle Nº	Adverse Event Resulting in Study Drug Discontinuation	Causality As Judged by PI
009	50	1	Cerebral Hemorrhage	Possibly Related
010	75	1	Myalgia, Edema, Asthenia, & Arthralgia	Possibly Related
012	75	2	Portacatheter Thrombosis	Possibly Related
013	100	0	Thrombotic Cerebrovascular Event	Possibly Related
014	50	3	Portacatheter Infection/Elevated Liver Enzymes	Not Related
016	50	2	Portacatheter Infection & Thrombosis	Not Related

There were no deaths on study.

Samples from all 16 patients were collected and tested for antibody formation using enzyme-linked immunosorbent assay (ELISA) and Western blot analyses. All patients received multiple doses of Neumega® and had sampling sufficient to permit the evaluation of antibody formation. Anti-rhIL-11 antibody formation was confirmed in only one subject.

Study C9305—Phase 1 Trial in Pediatric Patients

Study C9305 "*Phase 1/2 study of recombinant human interleukin eleven (NEUMEGA® rhIL-11 growth factor) at doses of 25, 50, and 75 µg/kg/d following ifosfamide, carboplatin, and etoposide (ICE) chemotherapy in pediatric patients with solid tumors or lymphoma*" is an ongoing open-label, non-randomized, dose-escalation study of doses of 25, 50, 75, and 100 µg/kg/d in pediatric patients. The trial opened in October 1994. An interim report on those patients enrolled through April 1996 was submitted.

Patients with confirmed pediatric solid tumors or lymphoma scheduled to receive at least two courses of ICE[D] were enrolled. The assigned Neumega® dose [E] was administered SQ, starting the day after chemotherapy and continuing until platelet recovery or to Day 28 (whichever came first). All patients received concurrent G-CSF 5 μg/kg/d. Standard dose-escalation criteria were utilized. Patients without progression could receive up to four additional cycles. The primary objective was the determination of the MTD and/or DLT.

Data on 23 patients, ranging in age from 8 months to 26 years, have been submitted. Twenty-two were ≤ 17 years old. The demographics are summarized below.

TABLE Nº 6—Study C9305: Patient Demographics

Demographic Characteristic		Dose of Neumega® (μg/kg/d)				*TOTAL (%) N=23*
		25 N=4	50 N=14	75 N=4	100 N=1	
Age (years):	Mean	10.1	8.41	4.7	2.0	*7.8*
	Median	6.5	6.0	5.0	2.0	*5.0*
	Range	1.5–26	0.7–17	0.9–8	N/A	*0.7–26*
Sex:	Male	1	10	2	1	*14 (61%)*
	Female	3	4	2	0	*9 (39%)*
Race:	Asian	1	0	0	0	*1 (4%)*
	Black	0	2	1	0	*3 (13%)*
	Caucasian	2	7	3	1	*13 (57%)*
	Hispanic	1	4	0	0	*5 (22%)*
	Other	0	1	0	0	*1 (4%)*

The 26 year old patient was allowed to participate because she had a pediatric tumor (astrocytoma). Exemptions were made for two patients < 1 year old. They were 10½ and 8 months old.

Five patients have received one cycle of treatment; 11 patients have received 2 cycles of treatment; one patient has received 3 cycles of treatment; 2 patients have received 4 cycles of treatment; 3 patients have received 5 cycles of treatment; and one patient has received 6 cycles of treatment. Neumega® has been well tolerated in this study. Most adverse events have been expected, mild to moderate in severity, and reversible.

[D] Ifosfamide 1.8 g/m²/d IV Days 1–5; Carboplatin 400 mg/m²/d IV Days 1&2; and VP-16 100 mg/m²/d IV Days 1–5, repeated every 21 days.

[E] There were weight requirements for the first two dose levels. For the 25 μg/kg/d dose patients must have weighed ≥20 kg. and for the 50 μg/kg/d dose patients must have weighed ≥ 10 kg. There was no minimum weight requirement for the 75 and 100 μg/kg/d dose levels.

Since there was no "Cycle 0" in this study, the interpretation of adverse events due to Neumega® was confounded by the effect of the chemotherapy.

The most frequently reported adverse event has been neutropenic fever, which was reported in 20 patients (87%). The incidence of neutropenic fever was similar across all dose groups, and in most cases was considered related to chemotherapy. Fifteen patients (65%) reported fever; vomiting was reported in 18 patients (78%); and diarrhea was reported in 15 patients (65%). These events were considered due to chemotherapy. Fifteen patients (65%) reported abdominal pain, which appeared to be related to the underlying disease or to the vomiting that resulted from the chemotherapy. Rhinitis and increased cough were reported in 15 (65%) and 13 (57%) patients, respectively. The rhinitis was considered related to the Neumega®. It was mild, and reversible upon discontinuation of dosing. Twelve patients (52%) reported nonspecific pain. The large number of patients reporting nonspecific pain was attributed to the age of the patients in this study, many of whom were unable to verbalize specific complaints. Sepsis was reported in 11 patients (48%), and also infection was reported in ten patients (43%). Rash and conjunctival injection were each reported in 10 patients. These events were mild and reversible. The most frequently reported cardiovascular adverse event was hypotension which was reported in 8 patients, and was generally associated with septic events. The adverse events most frequently reported by patients whose participation extended beyond 2 cycles were neutropenic fever and miscellaneous problems with central access devices, which were reported in six of seven patients (86%). Five patients (71%) each reported pain and rhinitis. Four patients (57%) each reported hypotension and pain.

To date, there appear to be no dose-limiting toxicities associated with Neumega® in this study. No significant differences among the four dosing groups in the incidence of any adverse clinical or laboratory event has been detected. Some adverse events that were common in the adult patient population, such as edema and dyspnea, were less common in the pediatric patients. In study C9206 edema was reported in 80% of the patients, whereas in this study only 22% of the patients reported edema. Dyspnea was reported in 48% of the patients in study C9206, but only 26% of the patients in this study reported dyspnea.

Twenty patients (87%) reported at least one grade 3 or 4 adverse event, and grade ≥ 3 adverse events occurred at all doses studied. The incidence of grade ≥ 3 adverse events did not appear to be dose-related. A total of 80 grade ≥ 3 events were reported during Cycles 1 and 2. The incidence of these events was similar at all doses studied. Fifty-five of the 80 events (69%) were judged to be not related to study drug. Of the remaining 25, nine (11%) were considered at least possibly related. The remaining 16 were judged to be of unknown relationship to study drug. The adverse events considered at least possibly related were fever, nervousness, abdominal pain, asthenia, anorexia, enlarged abdomen, pleural effusion, hemorrhage, and tachycardia. During subsequent cycles, a total of 17 grade ≥ 3 adverse events were reported in four patients, none of which was considered related to study drug.

All patients were reported to have at least one grade 3 hemoglobin (6.5-7.9 g/dL). Only one patient had a grade 4 hemoglobin value. No significant changes in prothrombin time

(PT) or partial thromboplastin time (PTT) were observed in any treatment group. Samples collected from 23 patients were analyzed by ELISA for the formation of antibodies to rhIL-11. The total exposure varied, but all patients except one received enough doses to permit an evaluation of antibody formation. Of the 22 patients, only one demonstrated a response indicative of antibody formation to the rhIL-11 drug product.

Three patients dropped out of the study because of an adverse event: Two because they developed Fanconi syndrome. The third patient had chemotherapy interrupted because of fever, and subsequent complications necessitated a change in regimen and study discontinuation. No patient had Neumega® stopped during a cycle, except in cases of disease progression or because of chemotherapy complications. Treatment with Neumega® was delayed in one patient because of thrombocytosis. There were no deaths on study.

III. NEUMEGA® AND BLOOD VOLUME IN NORMAL SUBJECTS

Background

As noted above, a mild anemia was noted in all normal animal species treated with rhIL-11 in the preclinical pharmacology studies. In study C9206 an anemia developed in all 12 patients who completed Cycle 0, and direct measurement of plasma volume and red blood cell (RBC) mass in three of the patients suggested that the hemoglobin decrease was predominantly due to an increase in plasma volume. In study C9305 all patients had at least one grade ≥3 hemoglobin value, although evaluation of anemia in this study was confounded by chemotherapy. To further study the anemia, two randomized, double-blind, placebo-controlled studies were conducted in normal volunteers.

Study C9314—Blood Volume & Na^+ Balance

Study C9314 "*An evaluation of changes in plasma volume and sodium balance, platelet activation, and activation of the coagulation system in healthy subjects receiving 25 µg/kg/d recombinant human interleukin eleven (NEUMEGA® rhIL-11 growth factor) or placebo*" was initiated in February 1994, and completed in April 1994. The primary objectives were to [1] compare changes in plasma volume and sodium balance in healthy volunteers receiving Neumega® with those in subjects receiving placebo and [2] further evaluate the safety of Neumega®. The secondary objectives were to [1] assess changes in platelet activation and activation of the coagulation system and [2] test for anti-IL-11 antibodies.

Six female (Group 1) and six male (Group 2) volunteers were selected for the study. Subjects in each group were randomized to receive either:

Neumega® 25 µg/kg SQ QD x7 days
—or—
Placebo.[F]

[F] Placebo was the vehicle, given in an equivalent volume/kg of body weight, by the same route and on the same schedule as the active drug.

Two separate randomizations were performed, one for each group, to either Neumega® or placebo. Each randomization was balanced regarding the number of subjects assigned to either active treatment or placebo. The placebo and Neumega® arms were balanced as to sex, age, height, and weight. All the subjects were Caucasian.

The subjects were healthy individuals whose body weight was within 10% of the range for their height as listed in the Metropolitan Life Insurance Company (MLIC) standard. They were confined and placed on a sodium-restricted diet (≤2 g/d) starting 2 days before dosing. They remained confined—on this diet—during the entire 7-day dosing period[G] and for 2 days after dosing was complete. Plasma volume, RBC mass, and urinary sodium excretion were determined at various times during the study. Platelet function was determined using routine aggregometry and measurement of the proportion of cells expressing the platelet activation antigen CD62 (P-selectin). The activity of the coagulation system was determined by measurements of fibrinopeptide A and prothrombin F_{1+2}. The primary endpoint was the percent change in plasma volume from baseline to Day 8. Urine electrolytes, serum electrolytes, renin, aldosterone, angiotensin, and antidiuretic hormones were measured to evaluate possible mechanisms for the changes in plasma volume and sodium balance. In addition to the platelet activation assay (CD62), platelet aggregometry, von Willebrand factor (vWF) multimer composition, and vWF antigen were evaluated. Platelet reticulocytes were also counted.

Hematology was evaluated at baseline, daily during dosing, and immediately post-dosing. Blood hemoglobin concentration decreased in all subjects. In the placebo group, mean hemoglobin decreased ~5% from baseline to Day 8. The decrease in the hemoglobin concentrations in the placebo group was attributed to repeated phlebotomy. In the Neumega® group, mean hemoglobin decreased ~15% from baseline to Day 8. The ~10% difference in the mean percent decrease in hemoglobin concentration between the two groups was statistically significant ($p < 0.01$). In each treatment group, the average decreases in hematocrit and RBC counts were similar to the average decreases in hemoglobin concentration. There was no significant change in the mean corpuscular volume of the RBCs during the study in either treatment group. Neither was there a change in the mean reticulocyte counts in either treatment group.

^{51}Cr-RBC mass and ^{125}I-plasma volume were determined at baseline and again at Day 8. Red blood cell mass decreased slightly in all subjects during the study. In the Neumega® group, mean RBC mass decreased from ~25 ml/kg at baseline to ~22 ml/kg at Day 8. In the placebo group, RBC mass decreased from ~29 ml/kg at baseline to ~24 ml/kg on Day 8. These decreases were not statistically different. Male and female subjects showed similar changes in RBC mass. The decrease in RBC mass in both the Neumega® and placebo groups was attributed to repeated phlebotomy for testing.

All subjects treated with Neumega® showed a >10% change in plasma volume at Day 8 compared to baseline, regardless of sex. None of the placebo-treated subjects had a

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[G] The 25 µg/kg/d dose and shorter dosing period (7 days) were selected to minimize any risk of Neumega® in normal subjects. The 25 µg/kg/d x7 day dosage schedule was considered adequate for study because [1] the hemoglobin decrease observed in study C9206 was not dose-related and [2] it developed during the first week of Neumega® administration.

change in their plasma volume greater than 10%. Mean plasma volume in the Neumega® group increased from ~44 ml/kg at baseline to ~55 ml/kg on Day 8. In the placebo group there was essentially no change (~50 ml/kg to ~52 ml/kg). A two-sided t-test was performed on the percentage change from baseline to test the null hypothesis there was no difference between the treatment groups. The null hypothesis was rejected with $p < 0.001$. The increase in mean plasma volume in the Neumega® group was associated with an increase in mean whole blood volume from ~77 ml/kg to ~86 ml/kg. A slight but insignificant increase in the mean whole blood volume was noted in subjects receiving placebo. The increase in mean whole blood volume was also statistically significant for subjects receiving Neumega® ($p < 0.01$). These data are summarized below.

TABLE № 7—Study C9314: Comparison of Hemoglobin & Blood Volume

Parameter		Treatment Group (Mean ± SD)		p-Value
		Neumega® N=6	Placebo N=6	
Hemoglobin (g/dL):	Baseline	14.0±1.0	13.9±1.4	
	Day 8	11.8±1.4	13.1±1.2	<0.01
	% Change	*-15.6±4.7*	*-5.5±1.7*	
Blood Volume (ml/kg):	Baseline	77.0±9.9	87.0±9.9	
	Day 8	86.4±13.1	88.2±8.9	<0.01
	% Change	*12.0±5.8*	*1.6±4.2*	
Plasma Volume (ml/kg):	Baseline	43.6±5.5	50.4±5.9	
	Day 8	54.8±9.9	51.6±5.5	<0.001
	% Change	*25.4±9.2*	*2.6±5.7*	
RBC Volume (ml/kg):	Baseline	25.4±2.9	28.5±3.4	
	Day 8	21.5±4.3	24.4±3.1	NS
	% Change	*-15.9±9.1*	*-14.3±5.5*	

Body weight, sodium excretion, and fluid balance were closely assessed. Body weights did not change significantly in either group during the study. The mean 24-hour urinary sodium excretion decreased in both groups from the prestudy collection through Day 2. There was a further decrease in sodium excretion in the female subjects on Day 3 (urine collections from the male subjects on Day 3 were inadvertently discarded). The 24-hour urine sodium excretion was less in the Neumega® group than in the placebo group on all days on which it was measured after the start of treatment. The difference in 24-hour sodium excretion between the Neumega® and placebo groups was statistically significant on Day 2 ($p < 0.02$). The difference was also significant on Day 3 ($p < 0.05$), although only data for the female subjects are available. The 24-hour urine potassium excretion also decreased in both groups. The average 24-hour urine potassium excretion during the first 3 days after baseline was lower in the Neumega® group than in the

placebo group. This difference was statistically significant for the excretion at Day 2. Net fluid balance was positive for all Neumega® subjects during the days of study drug dosing. Net fluid balance was variably positive or negative among the placebo-treated patients.

Mean plasma aldosterone concentrations increased in both groups from Day 1 to Day 4, and then decreased. The increase was greater in the placebo group than in the Neumega® group; however, this difference was not statistically significant. There were no significant changes in plasma angiotensin or renin from baseline.

Platelet function was measured using standard platelet aggregometry. There was no statistically significant difference in maximum platelet aggregation between the Neumega® group and the placebo group for any of the agonists tested. Platelet function was also assessed by flow cytometric analysis of P-selectin (CD62) expression. Two subjects in the Neumega® group had abnormally high spontaneous platelet activation (CD62 expression) on Day 8. However, despite these two subjects' results, there were no statistically significant changes from baseline in spontaneous platelet activation or activation in response to either concentration of ADP in either treatment group.

Plasma vWF concentration and multimer composition were normal in all subjects before study drug dosing. There was no significant change in the mean plasma vWF concentration from baseline to Day 8 in the placebo group. However, plasma vWF increased in every subject treated with Neumega®. The increase was statistically significant ($p < 0.01$). The mean plasma vWF concentration on Day 8 in the Neumega® group also was significantly higher than that in the placebo group ($p = 0.02$). The vWF multimer pattern remained normal in all subjects in both treatment groups throughout the study.

No significant changes were observed in the PT, PTT, prothrombin fragment F_{1+2}, or fibrinopeptide A in either treatment group. Plasma fibrinogen concentrations were normal in all subjects before study drug dosing. There was no significant change in mean fibrinogen concentration in the placebo group; however, plasma fibrinogen increased in all subjects treated with Neumega®. The increase was statistically significant ($p < 0.001$). The mean plasma fibrinogen concentration on Day 8 in the subjects receiving Neumega® also was significantly higher than that in the placebo group ($p < 0.001$). The changes in serum haptoglobin concentrations in the Neumega® group were similar to the changes in the plasma fibrinogen concentration. The increase in serum haptoglobin was also statistically significant ($p < 0.001$).

Mean serum iron concentrations decreased in both treatment groups. The mean serum ferritin concentration increased in the Neumega® group and decreased in the placebo group. The mean total iron-binding capacity decreased in both groups; the decrease in the Neumega® group was statistically significant ($p < 0.01$).

Study C9515—Effect of Diuretic on Hemoglobin Concentration

Study C9515 "*A study of the safety and effects of recombinant human interleukin eleven (rhIL-11) alone and in combination with hydrochlorothiazide/triamterene on hemoglobin concentration as an index of plasma volume in healthy volunteers*" was

performed to determine the effects of Neumega® and concurrent diuretic treatment on plasma-volume expansion in normal subjects. It was begun in August 1995 and completed in November 1995. The primary objective was to measure the effect of concurrent diuretic and Neumega® on the hemoglobin (Hgb) concentration (Hgb was to serve as an indicator of plasma volume). The secondary objectives were to assess the effect of Neumega® on urinary electrolyte levels, and to assess any carryover effect from one course of Neumega® to a subsequent course of Neumega®.

Twenty four normal subjects[H] were screened by being placed on a controlled (180 mEq Na^+ and 80 mEq K^+ per day) diet and having a 24-hour urine collected for Na^+ excretion. The 18 closest to the collective mean for 24-hour Na^+ excretion were selected—with allowances to obtain an equal distribution by sex—and randomized to one of six different study groups. The six study groups consisted of the three following treatments in different sequence: Neumega® 25 µg/kg/d SQ QD for 7 days; Placebo Neumega® SQ QD for 7 days; and Neumega® 25 µg/kg SQ QD plus Maxzide®-25[I] PO BID, both for 7 days.

Each study group consisted of three 7-day periods of administration of one of the above treatments. The first and second study drug periods were followed by 7-10 day washout periods. The six study groups are summarized below.

TABLE Nº 8—Study Groups for Study C9515

Study Group	Study Periods				
	Study Drug Period Nº 1	Washout Nº 1	Study Drug Period Nº 2	Washout Nº 2	Study Drug Period Nº 3
1	Neumega®	10-14 Days	Placebo	10-14 Days	Neumega®+ Maxzide®-25
2	Neumega®	10-14 Days	Neumega®+ Maxzide®-25	10-14 Days	Placebo
3	Placebo	10-14 Days	Neumega®+ Maxzide®-25	10-14 Days	Neumega®
4	Placebo	10-14 Days	Neumega®	10-14 Days	Neumega®+ Maxzide®-25
5	Neumega®+ Maxzide®-25	10-14 Days	Neumega®	10-14 Days	Placebo
6	Neumega®+ Maxzide®-25	10-14 Days	Placebo	10-14 Days	Neumega®

[H] The eligibility criteria were similar to those for study C9314, except the subjects' weight was to be within 15% of the MLIC standard, instead of 10%.

[I] Maxzide®-25 is a fixed-combination diuretic, consisting of hydrochlorothiazide 25 mg and triamterene 37.5 mg. There was no Maxzide®-25 placebo.

The subjects were randomly assigned to one of the six possible treatment sequences (*i.e.*, three subjects per treatment sequence). Subjects were placed on the controlled sodium and potassium diet 4 days before each dosing period, and the diet was maintained throughout each dosing period. The subjects were admitted to the investigational facility 2 days before each study period. Serum and urine electrolytes, serum and urine creatinine, and hemoglobin and hematocrit levels were monitored frequently, and subjects were discharged on Day 8 of each treatment period. The primary endpoint was the change in hemoglobin concentration over the 7-day dosing period. The secondary endpoints included urine volume, urinary sodium excretion, urinary potassium excretion, creatinine clearance, plasma osmolarity, and plasma electrolytes.

The demographic characteristics of the study population are given below.

TABLE Nº 9—Study C95 1 5: Subject Demographics

Demographic Characteristics		
Sex:	Male	9
	Female	9
Age (years):	Mean	30.4
	Range	21-49
Race:	Black	1
	Caucasian	12
	Hispanic	5
Height (cm):	Mean	172.6
	Range	160.0-191.0
Weight (kg):	Mean	67.6
	Range	48.0-86.2

Four of the 18 subjects withdrew from study. The subjects were combined by treatment group for the primary analysis. One subject, randomized to study group five, withdrew because of amblyopia on Day 1 of period 1 after receiving one dose each of Neumega® and Maxzide®-25. This subject was considered not evaluable for any of the treatment groups. A second subject, randomized to study group three, withdrew for personal reasons after receiving all seven doses of Neumega® in study period 1. This subject was evaluable only for the Neumega® treatment group. A third subject, randomized to study group six, withdrew for personal reasons after receiving the first Neumega® dose in study period 3. This subject was evaluable for the placebo and Neumega® + Maxzide®-25 treatment groups. The fourth subject, randomized to study group three, withdrew because of a family emergency prior to study period three. This subject was also evaluable only for the placebo and Neumega® + Maxzide®-25 treatment groups. The number of evaluable subjects by treatment group is summarized on the following page.

TABLE Nº 10—STUDY C9515: SUBJECT DISPOSITION FOR ANALYSIS

PURPOSE OF ANALYSIS	TREATMENT GROUP		
	PLACEBO	NEUMEGA®	NEUMEGA® + MAXZIDE®-25
BIOLOGIC ACTIVITY	17	14	16
SAFETY	17	15	17

AS IN PREVIOUS STUDIES, THE ADMINISTRATION OF NEUMEGA® RESULTED IN A >10% DECREASE IN HGB CONCENTRATION FROM BASELINE. THE DECREASE IN HGB WAS PARTIALLY AMELIORATED BY THE CONCURRENT ADMINISTRATION OF MAXZIDE®-25. THESE RESULTS ARE TABULATED BELOW.

TABLE Nº 11—STUDY C9515: EFFECT OF NEUMEGA® WITHOUT/WITH MAXZIDE®-25 ON HGB

TIME FROM FIRST DOSE	MEAN HGB (G/DL), ± SD		
	PLACEBO N=17	NEUMEGA® N=14	NEUMEGA® + MAXZIDE®-25 N=16
BASELINE (DAY -1)	14.4±0.9	14.5±1.2	14.4±1.1
2½ DAYS:	14.0±1.0	12.8±1.1	14.5±1.5
% CHANGE FROM BASELINE	*-2.9±3.6*	*-11.9±3.4*	*0.2±6.7*
7 DAYS:	14.3±1.0	12.7±1.0	13.6±1.0
% CHANGE FROM BASELINE	*-0.8±2.8*	*-12.6±3.6*	*-5.6±3.6*

THE DIFFERENCE IN HGB BETWEEN THE NEUMEGA® AND PLACEBO GROUPS WAS STATISTICALLY SIGNIFICANT ON BOTH THE 3RD ($p<0.01$) AND 7TH DAYS OF DOSING ($p<0.01$). THE DIFFERENCE BETWEEN THE NEUMEGA®+ MAXZIDE®-25 AND THE PLACEBO GROUPS WAS ALSO STATISTICALLY SIGNIFICANT ON DAY 7 ($p<0.05$). THE DIFFERENCE BETWEEN THE NEUMEGA® + MAXZIDE®-25 AND THE NEUMEGA® GROUPS WAS STATISTICALLY SIGNIFICANT ON DAY 7 ($p<0.01$). THERE WERE NO STATISTICALLY SIGNIFICANT EFFECTS OF DOSING, SEQUENCE, DOSING PERIOD, OR CARRYOVER FROM ONE DOSING PERIOD TO THE NEXT. THUS, NEITHER THE ORDER IN WHICH SUBJECTS RECEIVED STUDY TREATMENTS, NOR THE PERIOD IN WHICH THEY RECEIVED THEM, HAD AN EFFECT ON THE MAGNITUDE OF CHANGE IN HEMOGLOBIN CONCENTRATION.

FLUID BALANCE (INTAKE MINUS URINARY OUTPUT, NORMALIZED BY BODY WEIGHT), BODY WEIGHT, AND SERUM AND URINARY SODIUM AND POTASSIUM WERE ASSESSED FOR EACH GROUP. DURING DOSING WITH NEUMEGA® AND PLACEBO, POSITIVE FLUID BALANCE WAS MAINTAINED THROUGHOUT THE STUDY PERIOD. AFTER THE 7-DAY DOSING PERIOD, CUMULATIVE FLUID BALANCE IN THE NEUMEGA® GROUP WAS STATISTICALLY SIGNIFICANTLY DIFFERENT THAN THAT IN THE PLACEBO GROUP (2.6±1.7L *vs* 1.3±1.5L, RESPECTIVELY, $p<0.01$). A NEGATIVE FLUID BALANCE WAS NOTED INITIALLY IN THE NEUMEGA® + MAXZIDE®-25 GROUP; HOWEVER, THE BALANCE BECAME POSITIVE WITH CONTINUED DOSING. THE CUMULATIVE FLUID BALANCE IN THE NEUMEGA® + MAXZIDE®-25 GROUP WAS ALSO STATISTICALLY DIFFERENT THAN THAT IN THE NEUMEGA® GROUP (0.2±1.5L *vs* 2.6±1.7L,

RESPECTIVELY, $P<0.01$), BUT NOT THAN THAT IN THE PLACEBO GROUP. THERE WAS ESSENTIALLY NO CHANGE IN WEIGHT IN THE PLACEBO GROUP. SUBJECTS IN THE NEUMEGA® GROUP GAINED AN AVERAGE OF <1 KG, WHILE SUBJECTS IN THE NEUMEGA® + MAXZIDE®-25 GROUP LOST AN AVERAGE OF ~2 KG. THE CUMULATIVE SODIUM EXCRETION IN THE NEUMEGA® TREATMENT GROUP WAS 15% LESS THAN IN THE PLACEBO GROUP. THE DIFFERENCE WAS STATISTICALLY SIGNIFICANT ($P<0.01$). BOTH SODIUM AND POTASSIUM EXCRETION WERE SIGNIFICANTLY GREATER IN THE NEUMEGA® + MAXZIDE®-25 GROUP THAN IN EITHER THE NEUMEGA® OR PLACEBO GROUPS. THERE WAS NO SIGNIFICANT DIFFERENCE IN CREATININE CLEARANCE AMONG THE THREE GROUPS. THESE DATA ARE SUMMARIZED BELOW.

TABLE Nº 12—STUDY C9515: FLUID BALANCE, BODY WEIGHT, Na^+, & K^+

PARAMETER	TREATMENT GROUP		
	PLACEBO N=17	NEUMEGA® N=14	NEUMEGA® + MAXZIDE®-25 N=16
MEAN CUMULATIVE FLUID BALANCE ± SD (L)	1.3±1.5	2:6±1.7	0.2±1.5
MEAN WEIGHT CHANGE ± SD (KG):	-0.06±0.75	0.66±0.64	-1.95±1.15
% CHANGE FROM BASELINE	*-0.02±1.15*	*1.01±0.97*	*-2.88±1.60*
MEAN SERUM Na^+ ± SD (MEQ/L): BASELINE	142.8±2.3	143.5±2.4	142.6±2.4
DAY 7	142.9±2.1	142.1±2.4	139.8±1.9
% CHANGE FROM BASELINE	*0.06±1.67*	*-0.93±2.06*	*-1.95±1.85*
MEAN SERUM K^+ ± SD (MEQ/L): BASELINE	4.23±0.21	4.30±0.41	4.17±0.39
DAY 7	4.31±0.31	4.42±0.38	3.88±0.43
% CHANGE FROM BASELINE	*1.9±6.4*	*3.0±5.2*	*-6.4±11.2*
MEAN SERUM Cl^- ± SD (MEQ/L): BASELINE	103.7±1.8	104.0±2.3	103.3±1.7
DAY 7	103.9±2.3	103.0±1.6	94.2±3.3
% CHANGE FROM BASELINE	*0.25±2.41*	*-0.92±2.67*	*-8.76±3.43*
MEAN CUMULATIVE URINE Na^+ ± SD (MEQ/L)	982±193	833±154	1114±178
MEAN CUMULATIVE URINE K^+ ± SD (MEQ/L)	333±52	317±77	430±95

ADVERSE EVENTS IN NORMAL SUBJECTS

THE ADVERSE EVENTS (AES) REPORTED BY THE NORMAL VOLUNTEERS WERE FAIRLY SIMILAR TO THOSE REPORTED BY THE 13 PATIENTS STUDIED IN CYCLE 0 IN STUDY C9206.[J] NO AES IN EITHER STUDY WERE GRADED AS SERIOUS (GRADE 3) OR LIFE-THREATENING (GRADE 4). THE AES REPORTED BY TWO

[J] THE AES REPORTED BY MORE THAN ONE PATIENT IN STUDY C9206 WERE: FEVER (11), ASTHENIA (11), EDEMA (10), INJECTION SITE REACTIONS (9), RHINITIS (8), HEADACHE (6), MYALGIA (6), COUGH (4), INCREASED PLEURAL EFFUSION (3), VASODILATION (3), ABDOMINAL PAIN (3), DYSPNEA (2), HYPOTENSION (2), AND ARRHYTHMIA (2).

OR MORE SUBJECTS RECEIVING NEUMEGA® (INCLUDING THOSE RECEIVING CONCURRENT MAXZIDE ®-25) ARE TABULATED BELOW.

TABLE Nº 13—STUDIES C9314 & C9515: ADVERSE EVENTS

ADVERSE EVENT	TREATMENT ARM & STUDY				
	PLACEBO		NEUMEGA®		NEUMEGA® + MAXZIDE®-25
	C9314 N=6	C9515 N=17	C9314 N=6	C9515 N=15	C9515 N=17
INJECTED CONJUNCTIVA	0	1 (6%)	5 (83%)	11 (73%)	14 (82%)
HEADACHE	1 (17%)	1 (6%)	5 (83%)	7 (47%)	8 (47%)
NAUSEA	0	0	1 (17%)	4 (27%)	6 (35%)
ABDOMINAL PAIN	1 (17%)	0	3 (50%)	2 (13%)	4 (24%)
DIZZINESS	1 (17%)	1 (6%)	1 (17%)	2 (13%)	5 (29%)
SQ SITE REACTION	0	4 (24%)	0	5 (33%)	3 (18%)
FLU SYNDROME	0	0	0	3 (20%)	3 (18%)
VASODILATION	0	0	2 (33%)	3 (20%)	1 (6%)
ASTHENIA	1 (17%)	0	2 (33%)	2 (13%)	1 (6%)
EYE PAIN	0	0	0	3 (20%)	2 (12%)
VOMITING	0	1 (6%)	0	0	4 (24%)
PHARYNGITIS	1 (17%)	1 (6%)	0	2 (13%)	1 (6%)
DRY EYES	0	0	2 (33%)	0	1 (6%)
RHINITIS	1 (17%)	1 (6%)	1 (17%)	0	2 (12%)
BACK PAIN	0	1 (6%)	0	1 (7%)	2 (12%)
CHEST PAIN	0	1 (6%)	1 (17%)	0	2 (12%)
CONSTIPATION	0	1 (6%)	0	1 (7%)	1 (6%)
PAIN NOS	0	0	0	1 (7%)	1 (6%)
ANXIETY/NERVOUSNESS	0	0	1 (17%)	0	1 6%)
TACHYCARDIA	0	1 (6%)	0	0	2 (12%)
DYSPEPSIA	0	1 (6%)	0	0	2 (12%)

IN STUDY C9314, ANTI-IL-11 ANTIBODY WAS DETECTED IN SERUM DRAWN FROM ONE SUBJECT BEFORE STUDY DRUG DOSING BEGAN. THE TITER OF THE ANTIBODY DID NOT RISE AFTER DOSING. NO OTHER SUBJECTS HAD ANTI-RHIL-11 ANTIBODIES DETECTED. IN STUDY C9515, ANTIBODY FORMATION COULD BE EVALUATED IN ONLY 17 SUBJECTS. ALL 17 SAMPLES WERE NEGATIVE BY ELISA.

IV. PIVOTAL TRIAL Nº 1—STUDY C9308

General

Study C9308 "*Phase II double-blind, randomized study of recombinant human interleukin-11 (NEUMEGA® rhIL-11 growth factor) at doses of 25 and 50 µg/kg/d versus placebo in adult cancer patients with severe thrombocytopenia due to chemotherapy*" was a multicenter study conducted by 20 investigators in the United States. It opened for accrual in December 1993. The study was prematurely closed while still blinded in April 1995 because of slow accrual.

Study Design

The objectives of the study were: [1] to compare the activity of two doses of Neumega® with placebo in reducing the incidence of severe chemotherapy-induced thrombocytopenia and [2] to collect information on side effects, antibody production, and plasma rhIL-11 levels. Adult patients were required to [1] have a documented lymphoma or solid tumor, [2] have experienced severe thrombocytopenia in the cycle immediately prior to entry,[K] [3] have recovered to a platelet count ≥ 100,000/µL, and [4] be undergoing at least one more cycle of chemotherapy with the same regimen without dose reduction. Concurrent G-CSF was allowed with the subsequent cycle, but concurrent GM-CSF was not. (It was assumed essentially all patients would receive G-CSF.) Patients were stratified by: [1] bone marrow reserve function[L] and [2] duration of chemotherapy[M] and randomized to:

Neumega® 25 µg/kg
—or—
Neumega® 50 µg/kg
—or—
Placebo[N]

Since the chemotherapy regimens were not prospectively determined, and patients could have regimens of various lengths, the day following the completion of chemotherapy was designated as Day 1, and the days of chemotherapy were numbered negatively, counted backward from Day 1. There was no Day 0. The chemotherapy cycle prior to study entry was designated Cycle X. The first study cycle was designated Cycle X+1. Any succeeding cycles were numbered in sequence (*e.g.*, Cycle X+2, Cycle X+3, *etc*). Study

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[K] Defined as having received ≥ 1 platelet transfusion for a platelet count ≤20,000/µL which was felt to be due to chemotherapy. Patients who received platelet transfusions in other than the cycle prior to study entry were not eligible.

[L] Normal (no pelvic or lumbar radiation therapy and ≤ 1 prior chemotherapy regimen, including adjuvant) *vs* potentially-decreased (pelvic and/or lumbar radiotherapy and/or ≥2 previous chemotherapy regimens) marrow reserve.

[M] Shorter (≤2 day) *vs* longer (≥3 day) regimen.

[N] Patients randomized to placebo were re-randomized to receive a volume of 0.005 or 0.01 mL/kg, which were the two volumes of placebo equivalent to the two volumes of Neumega®.

drug was discontinued when a post-nadir platelet count ≥ 100,000/μL had been achieved or on Day 21, whichever came first.

Supportive care was kept constant from cycle X to cycle X+1, except that patients who did not receive G-CSF in cycle X could receive G-CSF in cycle X+1, if medically indicated. Platelet transfusions[o] were given for platelet counts ≤ 20,000/μL or for symptomatic bleeding. Hematology was obtained thrice weekly initially, and daily for ANC ≤ 500/μL or platelet count ≤ 50,000/μL. Patients who were to continue the same chemotherapy could receive Neumega® in cycle X+2 (and beyond) at the same dose (or equivalent by volume to placebo) in an open-label study.

The primary endpoints were [1] the requirement for one or more platelet transfusions and [2] toxicity (by WHO criteria). Secondary endpoints included the number of platelet transfusions required; the number of RBC transfusions required; the time to platelet independence; the time to platelet count ≥ 50,000/μL; and the time to platelet count ≥ 100,000/μL.

It was assumed that < 20% of patients would not require any platelet transfusion. It was calculated that it would require 30 evaluable patients per group (90 total) to detect a treatment difference of ≥ 40 percentage points between the placebo group and at least one of the Neumega® groups with power > 0.8 and type 1 error of 0.05. Patients who failed to receive a full course of Neumega® in cycle X+1 because of disease progression, toxicity not due to Neumega®, or a major protocol violation were to be excluded from the analysis of the primary endpoint, unless they required a platelet transfusion before discontinuing study drug—in which case they were considered treatment failures. It was estimated that 105 patients would need to be enrolled to yield 90 patients evaluable for statistical analysis.

Study Results—Efficacy

At the time the study was closed, total of 93 patients had been enrolled and randomized: 32 to the Neumega® 50 μg/kg/d arm; 31 to the Neumega® 25 μg/kg/d arm; and 30 to the combined placebo arm.[p]

The arms were reasonably well-balanced for various demographic characteristics. The median age of the study population was 47 years. Approximately half were male. About three-quarters were Caucasian. Almost all had an ECOG performance score of ≤ 1. The most common underlying diagnoses were: breast cancer 23 patients (25%); non-Hodgkin lymphoma 19 patients (20%); non-small cell lung cancer seven patients (8%); Hodgkin disease six patients (6%); small cell lung cancer five patients (5%); and ovarian cancer five patients (5%). Sixteen patients (17%) had various types of sarcoma.

The patients' demographic characteristics are summarized in the table on the next page.

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[o] Six units of pooled random-donor platelets or one single-donor apheresis unit.

[p] The two volumes of placebo were combined for the statistical analysis.

TABLE Nº 14—STUDY C9308: PATIENT DEMOGRAPHICS

DEMOGRAPHIC CHARACTERISTIC		STUDY ARM			TOTAL
		PLACEBO	NEUMEGA® 25 µG/KG/D	NEUMEGA® 50 µG/KG/D	
		N=30	N=31	N=32	N=93
AGE:	MEDIAN (YEARS)	46	51	45	47
	RANGE	18-66	17-73	23-68	17-73
SEX:	MALE	15 (50%)	12 (39%)	14 (44%)	41 (44%)
	FEMALE	15 (50%)	19 (61%)	18 (56%)	52 (56%)
RACE:	ASIAN	0	1 (3%)	2 (6%)	3 (3%)
	BLACK	2 (7%)	2 (6%)	2 (6%)	6 (6%)
	CAUCASIAN	25 (83%)	24 (77%)	27 (84%)	76 (82%)
	OTHER	3 (10%)	4 (13%)	1 (3%)	8 (9%)
ECOG PERFORMANCE SCORE:	0	20 (67%)	11 (35%)	17 (53%)	48 (52%)
	1	10 (33%)	17 (55%)	5 (17%)	42 (45%)
	2	0	3 (10%)	0	3 (3%)
DIAGNOSIS:	BREAST CANCER	9 (30%)	6 (19%)	8 (25%)	23 (25%)
	NON-HODGKIN LYMPHOMA	4 (13%)	5 (16%)	10 (31%)	19 (20%)
	NON-SMALL CELL LUNG CANCER	3 (10%)	3 (10%)	1 (3%)	7 (8%)
	HODGKIN DISEASE	2 (7%)	1 (3%)	3 (9%)	6 (6%)
	SMALL CELL LUNG CANCER	1 (3%)	2 (6%)	2 (6%)	5 (5%)
	OVARIAN CANCER	1 (3%)	3 (10%)	1 (3%)	5 (5%)
	MISCELLANEOUS	10 (33%)	11 (35%)	7 (22%)	28 (30%)
PRIOR THERAPY:	≤ 1 REGIMEN	16 (53%)	18 (58%)	19 (59%)	53 (57%)
	≥ 2 REGIMENS	14 (47%)	13 (42%)	13 (41%)	40 (43%)

THE PATIENTS ENROLLED RECEIVED TOTAL OF 24 DIFFERENT CHEMOTHERAPEUTIC REGIMENS. THE MOST COMMON REGIMENS WERE: DICEP (DOSE-INTENSE CYCLOPHOSPHAMIDE, ETOPOSIDE, AND CISPLATIN), 19 PATIENTS (20%); AND ICE (IFOSFAMIDE, CARBOPLATIN, AND ETOPOSIDE), 13 PATIENTS (14%). OTHER COMMONLY USED REGIMENS WERE DHAP (DEXAMETHASONE, HIGH-DOSE ARA-C, AND CISPLATIN); CYCLOPHOSPHAMIDE AND DOXORUBICIN; AND CARBOPLATIN ALONE—EACH USED IN EIGHT PATIENTS (9%); AND MAID (MESNA, DOXORUBICIN, IFOSFAMIDE, AND DACARBAZINE), FIVE PATIENTS (5%). THE GROUPS WERE SIMILAR IN TERMS OF THE SPECIFIC CHEMOTHERAPY AGENTS USED. THE CHEMOTHERAPY RECEIVED IS SUMMARIZED ON THE FOLLOWING PAGE.

TABLE Nº 15—STUDY C9308: CHEMOTHERAPY REGIMENS & DRUGS RECEIVED

CHEMOTHERAPY		STUDY ARM			TOTAL
		PLACEBO	NEUMEGA® 25 µG/KG/D	NEUMEGA® 50 µG/KG/D	
		N=30	N=31	N=32	N=93
REGIMEN:	DICEP	7 (23%)	6 (19%)	6 (19%)	19 (20%)
	ICE	5 (17%)	5 (16%)	3 (9%)	13 (14%)
	CARBOPLATIN	4 (13%)	3 (10%)	1 (3%)	8 (9%)
	CPA/DOX	4 (13%)	0	4 (13%)	8 (9%)
	DHAP	2 (7%)	0	6 (19%)	8 (9%)
	MAID	3 (10%)	2 (6%)	0	5 (5%)
	MISCELLANEOUS	5 (17%)	15 (48%)	12 (38%)	32 (34%)
AGENT:	ETOPOSIDE	14 (47%)	19 (61%)	19 (59%)	52 (56%)
	CYCLOPHOSPHAMIDE	12 (40%)	11 (35%)	14 (44%)	37 (40%)
	CISPLATIN	9 (30%)	7 (23%)	17 (53%)	33 (35%)
	IFOSFAMIDE	11 (37%)	10 (32%)	9 (28%)	30 (31%)
	CARBOPLATIN	11 (37%)	13 (42%)	5 (16%)	29 (31%)
	DOXORUBICIN	8 (27%)	4 (13%)	4 (13%)	16 (17%)
	ARA-C	2 (7%)	1 (3%)	6 (19%)	9 (10%)
	PACLITAXOL	3 (10%)	2 (6%)	1 (3%)	6 (6%)
	DACARBAZINE	3 (10%)	2 (6%)	0	5 (5%)
	FLUOROURACIL	1 (3%)	2 (6%)	0	3 (3%)
	THIOTEPA	0	1 (3%)	1 (3%)	2 (2%)
	MITOXANTRONE	0	1 (3%)	0	1 (1%)
DURATION:	≤2 DAYS	9 (30%)	9 (29%)	11 (34%)	29 (31%)
	3-5 DAYS	21 (70%)	22 (71%)	21 (66%)	64 (69%)

THE GROUPS WERE REASONABLY WELL-BALANCED AS TO THE NUMBER OF PLATELET TRANSFUSIONS RECEIVED DURING CYCLE X. MOST PATIENTS HAD NOT BEEN HEAVILY TRANSFUSED. OVER HALF OF THE PATIENTS HAD ONLY RECEIVED A SINGLE PLATELET TRANSFUSION IN CYCLE X: 16 IN THE PLACEBO ARM, 20 IN THE 25 µG/KG ARM, AND 15 IN THE 50 µG/KG ARM. THERE WAS A SLIGHT IMBALANCE (GIVEN THE SIZE OF THE ARMS) IN THE NUMBER OF PATIENTS WHO HAD RECEIVED FIVE OR MORE TRANSFUSIONS IN CYCLE X: FOUR IN THE PLACEBO ARM, THREE IN THE 25 µG/KG ARM, AND TWO IN THE 50 µG/KG ARM.

The study protocol stated the planned primary statistical analysis was to consist of comparing each Neumega® arm with placebo using a two-sided Fisher's Exact Test, with an adjustment made for the multiple comparisons. The protocol was silent with regards to the method of adjustment for multiplicity. According to the study report, the adjusted p-values for the primary analyses were calculated "*...using a bootstrap resampling method on binary data that were transformed through a Freeman-Tukey double arcsine transformation.*"

The sponsor conducted analyses on three populations: An intent-to-treat (ITT) population, an evaluable subgroup (ESG) population, and a completer subgroup (CSG) population. The protocol prospectively identified the primary analysis to be performed on the ESG population. The FDA confirmed the sponsor's analyses of the three populations, and performed additional, exploratory analyses on the ESG and ITT populations. Exploratory analyses were not performed on the CSG population since, while this type of analysis may provide an estimate of a study drug's performance on a study endpoint under "ideal" circumstances, it may not provide a reliable estimate of a study drug's performance in the "real world" clinical setting, where the patients that will be able to complete the intended course of therapy cannot be identified prospectively—and where the drug's effect on the patient (*E.G.*, treatment failure and/or toxicity) must be considered.

Eleven patients were considered by the sponsor to be not evaluable for the primary (ESG) analysis. These patients are tabulated below.

TABLE Nº 16—Study C9308: Patients Not Evaluable for Primary Analysis

Study Arm (N)	Reason for Exclusion from Analysis of Primary Endpoint	Platelet Transfusion?
Placebo (N=30)	Major Protocol Violation: Chemotherapy Dose Reduction	No
	Major Protocol Violation: Transfused with Platelet Count 22,000/μL	Yes
	Ineligible: Baseline Platelet Count < 100,000/μL (13,000/μL)	Yes
25 μg/kg (N=31)	Consent Withdrawn: Did Not Receive Study Drug	Yes
	Consent Withdrawn: Did Not Receive Study Drug	Yes
	Major Protocol Violation: Cycle X+1 Chemotherapy Dose-Reduced	No
50 μg/kg (N=32)	Major Protocol Violation: Not Transfused with Platelet Count 14,000/μL	No
	Consent Withdrawn: Did Not Receive Study Drug	No
	Consent Withdrawn: Did Not Receive Study Drug	No
	Consent Withdrawn: Did Not Receive Study Drug	No
	Protocol Violation: Transfused with Platelet Count 27,000/μL	Yes

Thus, there were 27 patients in the placebo arm, 28 patients in the 25 μg/kg arm, and 27 patients in the 50 μg/kg arm considered evaluable for the primary analysis. Of these,

one (4%), five (18%), and eight (30%) patients, respectively, did not require a platelet transfusion in Cycle X+1. The difference between the placebo arm and the 50 μg/kg arm was statistically significant (p=0.02 by Fisher's Exact Test). The adjusted p-value was also 0.02 when adjusted by the bootstrap method. The difference between placebo and 25 μg/kg was not statistically significant (p=0.19 by Fisher's Exact Test). These data are tabulated below.

TABLE Nº 17—Study C9308: Results of Primary Analysis

Received Platelet Transfusion	Study Arm		
	Placebo N=27	25 μg/kg N=28	50 μg/kg N=27
No	1 (4%)	5 (18%)	8 (30%)
Yes	26 (96%)	23 (82%)	19 (70%)

A series of exploratory analyses were performed by the sponsor on the ESG population. Neither age nor sex had a significant influence on outcome. None of the chemotherapy regimens was used frequently enough to allow reliable subset analyses—although none of the 19 patients receiving the DiCEP regimen avoided platelet transfusions, and only one of 12 evaluable patients receiving the ICE regimen avoided platelet transfusions. The results did suggest patients with less prior therapy (no pelvic or lumbar radiation therapy and ≤ 1 previous chemotherapy regimen) and a shorter chemotherapy regimen (≤ 2 days) were more likely to avoid platelet transfusion. The only cancer diagnosis that appeared to influence outcome was non-Hodgkin lymphoma since none of the 18 patients avoided platelet transfusion. However, the study was not planned with sufficient power to detect differences in outcome among patients in the various strata and substrata.

On FDA's review of the case report forms (CRFs) submitted it was felt that two patients (003 and 022), both randomized to the Neumega® 50 μg/kg arm, could possibly be classified differently for analysis.

- ☒ Patient 003 was excluded from the primary analysis because of a major protocol violation—not being transfused with a platelet count <20,000/μL. The study protocol stated "*All patients will be evaluable for the primary endpoint except...those for which a major protocol violation occurred during treatment...patients who require a platelet transfusion before experiencing one of the events described above will still be counted as failures in the analysis of the primary endpoint.*" This patient could be considered evaluable. The patient did require platelet transfusion by the terms of the protocol (*i.e.*, platelet count ≤20,000/μL), and the protocol violation event (*i.e.*, failure to transfuse) occurred afterwards. Thus, this patient could be classified in the analysis as a "failure" (*i.e.*, having been transfused).

- ☒ Patient 022 was included in the analysis in spite of a 9-day gap in platelet counts from Day +9 to Day +18. This 9-day gap in platelet counts could be considered a major protocol violation, and render the patient not evaluable, since the patient

conceivably could have dropped below 20,000/μL during this period.[o] Thus, the ability to fully evaluate this patient was compromised by the 9-day hiatus in counts.

If patient 003 is included in the analysis as a "failure" and patient 022 is excluded from the statistical analysis as "not evaluable" the unadjusted p-value for the difference between the placebo arm and the 50 μg/kg arm increases slightly to 0.05.[R] Since this reclassification only involved the 50 μg/kg arm, the p-values for the 25 μg/kg arm do not change.

The sponsor's ITT analysis included all 93 patients randomized. This patient population included the five patients who withdrew consent and never received study drug. Minimal clinical data are available on these patients. All did receive chemotherapy, although two received reduced doses (one in each Neumega® arm). One patient in the 25 μg/kg arm, did have three platelet counts documenting a platelet count <20,000/μL. The other four patients only had a single platelet count documented, which occurred 1 ½-2 weeks after completion of chemotherapy. Both of the patients in the 25 μg/kg arm received platelet transfusions. The three patients in the 50 μg/kg arm have no record of receiving platelet transfusions.

According to the sponsor's ITT analysis two patients (7%) in the placebo arm, six patients (19%) in the 25 μg/kg arm, and 12 patients (38%) in the 50 μg/kg arm did not receive platelet transfusions. Comparison of the differences between placebo and the 25 μg/kg arm and the placebo arm and the 50 μg/kg arm yielded unadjusted p-values of 0.26 and 0.005, respectively, by Fisher's Exact Test. The adjusted p-value for the comparison of the placebo and 50 μg/kg arms was 0.006. The data are summarized below.

TABLE Nº 18—Study C9308: Sponsor's ITT Analysis on All Randomized Patients

Platelet Transfusion Received	Study Arm		
	Placebo N=30	25 μg/kg N=31	50 μg/kg N=32
No	2 (7%)	6 (19%)	12 (38%)
Yes	28 (93%)	25 (81%)	20 (62%)

One of the benefits of the ITT analysis is that it is usually a more conservative analysis. However, the inclusion of the five patients who never received study drug adds three "successes" to the 50 μg/kg arm and none to placebo. Thus, a more conservative method to conduct the ITT analysis on all randomized patients would be to consider all five of

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[o] This patient received the first of four platelet transfusions in Cycle X on Day +9. The platelet counts recorded in Cycle X+1 were: Day +1—165,000/μL; Day +3—129,000/μL; Day +5—73,000/μL; Day +9—62,000/μL; and Day +18—101,000/μL.

[R] Since the best method of—or even the need for—adjusting p-values for multiplicity remains the subject of debate among statisticians, for the sake of simplicity only unadjusted p-values will be reported for the FDA's exploratory analyses.

THE PATIENTS WHO DID NOT RECEIVE STUDY DRUG AS "FAILURES" (*I.E.*, HAVING A PLATELET TRANSFUSION), SINCE THE DATA ARE REALLY NOT ADEQUATE TO CONCLUDE THAT THE THREE PATIENTS FOR WHOM DOCUMENTATION OF PLATELET TRANSFUSION IS LACKING, IN FACT WERE NOT TRANSFUSED. THE RESULT OF THIS "CONSERVATIVE" EXPLORATORY ITT ANALYSIS IS GIVEN BELOW.

TABLE Nº 19—"CONSERVATIVE" ITT ANALYSIS ON ALL RANDOMIZED PATIENTS

PLATELET TRANSFUSION RECEIVED	STUDY ARM		
	PLACEBO N=30	25 μG/KG N=31	50 μG/KG N=32
NO	2 (7%)	6 (19%)	9 (28%)
YES	28 (93%)	25 (81%)	23 (72%)

THE UNADJUSTED P-VALUE FOR THE COMPARISON OF THE PLACEBO AND 50 μG/KG ARMS FOR THIS ANALYSIS WAS 0.04. IF THE ANALYSIS IS REPEATED RECLASSIFYING PATIENT 003 AS IF SHE HAD BEEN TRANSFUSED AS PER PROTOCOL, THE UNADJUSTED P-VALUE FOR THE COMPARISON OF THE PLACEBO ARM AND THE 50 μG/KG ARM BECOMES 0.08. THE P-VALUES FOR THE COMPARISON OF THE PLACEBO AND 25 μG/KG ARMS AGAIN REMAIN UNCHANGED.

AN ALTERNATIVE METHOD OF PERFORMING THE ITT ANALYSIS WOULD BE TO SIMPLY EXCLUDE THOSE PATIENTS WHO NEVER RECEIVED STUDY DRUG. THIS EXPLORATORY ANALYSIS IS GIVEN BELOW.

TABLE Nº 20—STUDY C9308: ITT ANALYSIS ON PATIENTS RECEIVING STUDY DRUG

PLATELET TRANSFUSION RECEIVED	STUDY ARM		
	PLACEBO N=30	25 μG/KG N=29	50 μG/KG N=29
NO	2 (7%)	6 (21%)	9 (31%)
YES	28 (93%)	23 (79%)	20 (69%)

FOR THIS ANALYSIS, COMPARISON OF THE DIFFERENCES BETWEEN PLACEBO AND THE 25 μG/KG ARM AND PLACEBO AND THE 50 μG/KG ARM YIELDED UNADJUSTED P-VALUES OF 0.15 AND 0.02, RESPECTIVELY. IF THE ANALYSIS IS REPEATED RECLASSIFYING PATIENT 003 AS IF SHE HAD BEEN TRANSFUSED AS PER PROTOCOL, THE UNADJUSTED P-VALUE FOR THE COMPARISON OF THE PLACEBO ARM AND THE 50 μG/KG ARM BECOMES 0.04. THE P-VALUES FOR THE COMPARISONS OF THE PLACEBO ARM AND THE 25 μG/KG ARM REMAIN UNCHANGED.

FDA ATTEMPTED AN EXPLORATORY ANALYSIS BY CENTER ON ALL THE PATIENTS WHO HAD RECEIVED AT LEAST ONE DOSE OF STUDY DRUG (N=88). FOR THIS, AND SUBSEQUENT, ANALYSES PATIENT 003 WAS CONSIDERED TO HAVE BEEN TRANSFUSED. THE ANALYSIS BY CENTER WAS COMPLICATED BY SEVERAL CONSIDERATIONS. PATIENT ACCRUAL VARIED CONSIDERABLY BY CENTER. TWO CENTERS ACCRUED 19 PATIENTS EACH; ONE CENTER ACCRUED SEVEN PATIENTS; TWO CENTERS ACCRUED SIX PATIENTS EACH; THREE CENTERS ACCRUED FOUR PATIENTS EACH; TWO CENTERS ACCRUED THREE PATIENTS EACH; FIVE CENTERS ACCRUED TWO PATIENTS EACH; AND THREE CENTERS ACCRUED ONE

patient each. Since the randomization was not stratified by site, there were imbalances between the study arms within centers. Only six centers had at least one patient in both the placebo and 50 μg/kg arms. The incidence of platelet transfusion also varied markedly between centers. In the two largest centers, the transfusion rates were 100% (19/19) and 89% (17/19). In the center in which all the patients required platelet transfusion, all patients received DICEP. In the other center, about half of the patients received the ICE regimen. One of the two patients who avoided transfusion had dose reduction in Cycle X+1 (which was a major protocol violation). In the 3rd largest center the transfusion rate was 29% (2/7). Patients in this center received six different regimens, and only three patients had an ANC ≤500/μL. In the 4th and 5th largest centers the transfusion rate was 100% (6/6). Of the centers remaining (all with four or less patients) only two had a patient in both the placebo and Neumega® arms. In both centers the transfusion rate was 100%. Thus, any center-specific effect seen in this analysis could also have been due to the specific chemotherapy regimen(s) used..

Since no patient who received the DICEP regimen avoided platelet transfusion, and only two patients (one of whom had chemotherapy dose reduction) who received the ICE regimen avoided transfusion, the possibility that Neumega® might be ineffective following very myelosuppressive regimens was investigated. For this exploratory analysis, the degree of myelosuppression was measured by the time to neutrophil recovery, defined as the time to ANC ≥500/μL in Cycle X+1 (the data were not available for Cycle X). Eighty-seven patients had data adequate to determine the time to ANC ≥500/μL. All but three of these patients (one in the 25 μg/kg arm and two in the 50 μg/kg arm) received concurrent G-CSF. A logistic regression was used in *S-PLUS* to model the probability of receiving a platelet transfusion using time to ANC ≥500/μL as a covariate. The analysis suggested time to ANC ≥500/μL was an important covariate ($p<0.01$) where long times to ANC ≥500/μL corresponded to a greater need for platelet transfusion. After adjusting for this covariate, another logistic regression analysis confirmed the treatment effect remained when comparing the 50 μg/kg arm with placebo.

The time to ANC ≥500/μL ranged between 0 and 20 days for the 87 patients. The study population was arbitrarily divided into two approximately equal groups—those in whom time to ANC ≥500/μL was ≤10 days (N= 43) and those in whom time to ANC ≥500/μL was ≥11 days (N=44). The incidence of platelet transfusion was evaluated for each group. These data summarized below.

TABLE Nº 21—Study C9308: Analysis by Time to Neutrophil Recovery

Time to ANC ≥500/μL	Platelet Transfusion Received	Study Arm		
		Placebo	Neumega® 25 μg/kg	Neumega® 50 μg/kg
≤10 Days N=43	Yes	13 (87%)	10 (67%)	7 (54%)
	No	2 (13%)	5 (33%)	6 (46%)
≥11 Days N=44	Yes	15 (100%)	13 (93%)	13 (87%)
	No	0 (0%)	1 (7%)	2 (13%)

This exploratory analysis would suggest that the treatment effect of Neumega® was not distinctly seen with highly myelosuppressive regimens (arbitrarily defined as a regimen which results in a time to ANC ≥500/μL of ≥ 11 days).

The number of platelet transfusion events and time to platelet recovery were secondary endpoints. Patients received either random-donor platelets or single-donor platelets. There was a slight imbalance in the type of platelet product received. Forty-two percent of the patients in the placebo arm and 44% of the patients in the 25 μg/kg arm received single-donor platelets compared to 18% of the patients in the 50 μg/kg arm.

The FDA's analysis of transfusion events was based on 87 patients for whom platelet transfusion data were available. The median number of platelet transfusion events was 2.5 in the placebo arm, two in the 25 μg/kg arm, and one in the 50 μg/kg arm. The mean number of platelet transfusion events was 3.3 for the placebo arm, 2.0 for the 25 μg/kg arm, and 2.2 for the 50 μg/kg arm. The differences were not statistically significant. These data are summarized below.

TABLE Nº 22—Study C9308: Platelet Transfusions in Cycle X+1

Platelet Transfusion Events	Study Arm		
	Placebo N=30	25 μg/kg N=29	50 μg/kg N=28
Median	2.5	2	1
Mean	3.4	2.1	2.2
Range	0-17	0-7	0-9
Total Number of Transfusions:	91	59	60
% Single-Donor Units	42%	44%	18%

Three-fourths (74%) of the 88 patients who received study drug were transfused for each platelet count ≤20,000/μL as per protocol: 24 in the placebo arm; 19 in the 25 μg/kg arm; and 22 in the 50 μg/kg arm. Twelve patients missed one transfusion; eight patients missed two transfusions; two patients missed four transfusions; and one patient missed six transfusions. Thus, there were 42 documented instances in which a platelet transfusion was not given for a platelet count ≤20,000/μL: eight in the placebo arm; 14 in the 25 μg/kg arm; and 20 in the 50 μg/kg arm. If these "missed" platelet transfusions are also considered transfusion events, the data are not significantly changed. The median numbers are unchanged and the mean number of platelet transfusion "events" become 3.6, 2.5, and 2.8, respectively.

Two patients, both in the 50 μg/kg arm, did not recover to a platelet count ≥20,000/μL. According to the sponsor's ESG analysis of time to platelet recovery, the median time to platelet recovery to ≥20,000/μL was 17 days, 14½ days, and 13 days in the placebo, 25 μg/kg arm, and 50 μg/kg arm, respectively. The FDA analysis was done on all patients for whom there were data, including those considered not evaluable but

EXCLUDING THE FIVE PATIENTS WHO NEVER RECEIVED STUDY DRUG. THE MEDIAN TIME TO RECOVERY, WHICH WAS DETERMINED FROM THE KAPLAN-MEIER ESTIMATES OF TIME TO RECOVERY, DIFFERED SLIGHTLY FROM THE SPONSOR'S ANALYSIS—15 DAYS, 13 DAYS, AND 13 DAYS, RESPECTIVELY. THE DIFFERENCES IN THE ARMS WERE NOT STATISTICALLY SIGNIFICANT IN EITHER ANALYSIS. THESE DATA ARE TABULATED BELOW.

TABLE Nº 23—STUDY C9308: TIME TO PLATELET RECOVERY TO ≥20,000/μL

ANALYSIS	STUDY ARM					
	PLACEBO		25 μG/KG		50 μG/KG	
	N	MEDIAN	N	MEDIAN	N	MEDIAN
SPONSOR (N=80)	27	17.0 DAYS	28	14.5 DAYS	25	13.0 DAYS
FDA (N=87)	30	15.0 DAYS	28	13.0 DAYS	29	13.0 DAYS

A TOTAL OF 19 PATIENTS (20%) DID NOT COMPLETE CYCLE X+1 AS PLANNED: TWO IN THE PLACEBO ARM (7%), FIVE IN THE 25 μG/KG ARM (16%), AND 12 IN THE 50 μG/KG ARM (38%). IN ADDITION TO THE FIVE PATIENTS WHO WITHDREW BEFORE RECEIVING STUDY DRUG, EIGHT PATIENTS WITHDREW BECAUSE AN ADVERSE EVENT (AE) AND SIX PATIENTS WITHDREW FOR A REASON OR REASONS NOT ATTRIBUTABLE TO A SPECIFIC AE. OF THE EIGHT PATIENTS WHO WITHDREW BECAUSE OF A SPECIFIC AE: ONE PATIENT IN THE PLACEBO ARM WITHDREW BECAUSE OF THROMBOCYTHEMIA AND ONE BECAUSE OF PHLEBITIS AND CELLULITIS; TWO PATIENTS IN THE 25 μG/KG ARM WITHDREW BECAUSE OF ATRIAL FIBRILLATION (AF); AND ONE PATIENT EACH IN THE 50 μG/KG ARM WITHDREW BECAUSE OF AF, AN UNSPECIFIED ARRHYTHMIA, SYNCOPE, AND FLU-LIKE SYMPTOMS. OF THE SIX PATIENTS WHO WITHDREW NOT BECAUSE OF A SPECIFIC AE: ONE WITHDREW BECAUSE OF RAPIDLY PROGRESSIVE DISEASE; ONE, WHO WAS HOSPITALIZED WITH PANCYTOPENIA, WITHDREW TO "*...VISIT FAMILY...*;" ONE, WHO WAS HOSPITALIZED WITH AF, WITHDREW BECAUSE OF "*...TOO MANY SIDE EFFECTS, INCLUDING EDEMA...*;" AND THREE WITHDREW CONSENT FOR REASONS NOT STATED. OF THESE THREE, ALL THREE WERE NOTED TO DEVELOP AF: ONE WAS HOSPITALIZED AND THE OTHER TWO RESOLVED SPONTANEOUSLY. THUS, 28 PATIENTS FROM THE PLACEBO ARM, 26 FROM THE 25 μG/KG ARM, AND 20 FROM THE 50 μG/KG COMPLETED CYCLE X+1. CYCLE X+1 PATIENT WITHDRAWAL IS SUMMARIZED BELOW.

TABLE Nº 24—STUDY C9308: RANDOMIZED PATIENTS WHO DID NOT COMPLETE CYCLE X+1

STUDY DRUG DISCONTINUATION	STUDY ARM			*TOTAL*
	PLACEBO	NEUMEGA® 25 μG/KG/D	NEUMEGA® 50 μG/KG/D	
	N=30	N=31	N=32	*N=93*
BEFORE DOSING	0	2	3	*5*
DURING DOSING: DUE TO AE	2	2	4	*8*
NOT DUE TO AE	0	1	5	*6*
TOTAL	*2*	*5*	*12*	*19*

Twenty-eight patients elected to proceed to Cycle X+2: 10 from the placebo arm, 11 from the 25 μg/kg arm, and seven from the 50 μg/kg arm. Five patients in the placebo group who entered Cycle X+2 had received the lower volume placebo and five had received the higher volume placebo. These were assigned to the 25 μg/kg dose and the 50 μg/kg dose arms, respectively. Patients who continued into the open-label cycle were treated with the same chemotherapy they received in Cycle X+1 with no dose reduction—except for one patient who was excluded from the analyses. Four patients did not require platelet transfusion in Cycle X+2: three had received Neumega® and did not require platelet transfusion in Cycle X+1 (one in the 25 μg/kg arm and two in the 50 μg/kg arm). The fourth patient received placebo and was transfused in Cycle X+1.

Study Results—Safety

The 88 patients who received at least one dose of study drug were included in the safety analysis. The incidence of AEs in each of the study arms was compared[S] by Fisher's Exact Test. The incidence of AEs in the Neumega® arms was similar,[T] and the two arms were combined for analysis. The AEs associated with Neumega® ($p<0.1$ by Fisher's Exact Test) are summarized below. For the AEs marked with an asterisk (*) the p-value was <0.05.

TABLE Nº 25—Study C9308: AEs Associated with Neumega® in Cycle X+1

Adverse Event	Study Drug			
	Placebo N=30		Neumega® N=58	
	Overall	Grade ≥3	Overall	Grade ≥3
Edema*	5 (17%)	0	35 (60%)	1 (2%)
Dyspnea	8 (27%)	1 (3%)	28 (48%)	3 (5%)
Anorexia	6 (20%)	0	23 (40%)	0
Fever	6 (20%)	2 (7%)	22 (38%)	2 (3%)
Headache*	2 (7%)	0	18 (31%)	1 (2%)
Tachycardia*	0	0	14 (24%)	0
Palpitations*	0	0	11 (19%)	0
Atrial Fibrillation/Flutter*	0	0	8 (14%)	1 (2%)
"Serious" Anemia	0	0	6 (10%)	6 (10%)

[S] Placebo *vs* 25 μg/kg, placebo *vs* 50 μg/kg, and 25 μg/kg *vs* 50 μg/kg.

[T] Except for injection site reactions, syncope, and constipation. Both injection site reactions and constipation were more common in the 25 μg/kg arm; however, the overall incidences were similar to those of placebo (9% *vs* 13% and 19% *vs* 13%, respectively). Syncope was reported in five patients (17%) in the 50 μg/kg arm, none of the patients in the 25 μg/kg arm, and in one patient (3%) in the placebo arm. The only statistically significant difference was the difference between the two Neumega® arms ($p=0.05$).

Of the eight patients with AF, two had a history of atrial arrhythmias during Cycle X and had similar arrhythmias during Cycle X+1 and two had atrial arrhythmias detected only by Holter monitoring. A retrospective logistic regression analysis of possible risk factors for atrial arrhythmias was performed in 68 patients (including ten placebo patients who received Neumega® in Cycle X+2). Age was the only factor significantly associated with the likelihood of developing atrial fibrillation or flutter.

There was a dose-response effect in the incidence of serious AEs. Fifteen patients had at least one AE judged to be serious: two (7%) in the placebo arm; four (14%) in the Neumega® 25 μg/kg arm; and nine (31%) in the Neumega® 50 μg/kg arm. The difference was statistically significant (p=0.02 by the Cochran-Armitage Test).

The increase in "serious" (WHO grade ≥3) anemia in the patients receiving Neumega® was due to the fact that the mean Hgb concentration at baseline was significantly lower in both the Neumega® arms than in the placebo arm (p = 0.03). Overall, mean hemoglobin concentrations decreased similarly in all three arms during Cycle X+1. The decreases were more pronounced during the first 5 days of treatment among patients receiving Neumega® compared with the patients receiving placebo. However, in all three arms the Hgb nadir occurred on Day 7 and the decrease from baseline was similar (14% for the placebo arm; 11% for the 25 μg/kg arm; and 15% for the 50 μg/kg arm). By the end of Cycle X+1, median Hgb concentrations were essentially identical in the three arms, even though the Neumega® arms started lower. These data are summarized below.

TABLE Nº 26—Study C9308: Mean Hgb Concentrations in Cycle X+1

Study Arm	Mean Hgb Concentration (g/dl) on Study Day (Cycle X+1)						
	0	3	5	7	14	21	26
Placebo	10.9	11.0	10.3	9.4	10.2	10.2	10.1
Neumega®: 25 μg/kg	10.3	9.9	9.3	9.2	9.9	10.5	10.0
50 μg/kg	10.2	9.5	9.1	8.7	9.6	9.8	10.0
Combined	10.3	9.7	9.2	9.0	9.7	10.2	10.0

Red blood cell transfusion was similar in the three arms. Twenty-six patients (87%) in the placebo arm, 26 patients (90%) in the 25 μg/kg arm, and 24 patients (83%) in the 50 μg/kg arm received RBC transfusions. The median number of RBC transfusion events was two in each of the three arms. The mean numbers of RBC transfusion events were 2.0, 2.2, and 2.0 for the placebo, 25 μg/kg, and 50 μg/kg arms, respectively. The median numbers of RBC units transfused were two, four, and two in the placebo, 25 μg/kg, and 50 μg/kg arms, respectively. The mean numbers of RBC units transfused events were 3.0, 3.2, and 3.1 for the placebo, 25 μg/kg, and 50 μg/kg arms, respectively.

The total number of transfusion events of any kind (RBC, platelet, and "missed" platelet) was also compared among the study arms. The median numbers of transfusion events of any kind were five in the placebo arm; five in the 25 μg/kg arm; and four in the 50 μg/kg

arm. The mean numbers of transfusion events of any kind were 5.6 in the placebo arm; 4.8 in the 25 µg/kg arm; and 4.9 in the 50 µg/kg arm.

There was no evidence of an adverse effect on neutrophil recovery (*e.g.*, "lineage steal") or of an adverse drug interaction with G-CSF (all but three patients received concurrent G-CSF). The time to ANC ≥500/µL was similar in the three arms, as was the incidence of febrile neutropenia. As with platelet recovery, the FDA's analysis differed slightly from the sponsor's analysis. These data are summarized below. One patient in the 25 µg/kg arm did not recover to an ANC ≥500/µL.

TABLE Nº 27—Study C9308: Neutrophil Recovery

Parameter		Study Arm		
		Placebo N=30	25 µg/kg N=28	50 µg/kg N=29
Days to ANC ≥500/µL (FDA's Analysis):	Median	11.0	10.5	11.0
Days to ANC ≥500/µL (Sponsor's Analysis):	Median	12.5	13.0	12.0
	Mean	11.2	10.0	10.0
	Range	0-20	0-21	0-21
Febrile Neutropenia		9 (30%)	8 (28%)	11 (38%)
Concomitant G-CSF		30 (100%)	27 (96%)	27 (93%)

One patient in the 25 µg/kg arm died after 7 days of treatment in Cycle X+2. No other patient died while being treated with study drug; however, seven patients died during or within 3 months of entering the study. The deaths were equally distributed among the three arms: two in the placebo arm and three in each of the Neumega® arms. All deaths were due to cancer progression, and were considered unrelated to treatment with study drug.

Of the 88 patients who received study drug, 85 had samples suitable for assessing antibody formation. Increased reactivity in the antibody ELISA was observed in samples from six patients (7%). The development of anti-rhIL-11 antibodies appeared to have no clinical significance—*i.e.*, the antibodies were not associated with any adverse events.

V. Pivotal Trial Nº 2—Study C9416

General

Study C9416 "*Phase 2 double-masked, randomized comparison of recombinant human interleukin eleven (Neumega® rhIL-11 growth factor) at a dose of 50 µg/kg/d plus G-CSF vs placebo plus G-CSF in patients with breast cancer receiving high-dose cyclophosphamide and doxorubicin*" was conducted by 14 investigators in the United States. The trial opened for accrual in November 1994 and closed in May 1996.

Study Design

The study objectives were to assess: [1] the ability of Neumega® to prevent platelet transfusion over two cycles of chemotherapy; [2] the toxicity of Neumega®; and [3] the production of anti-rhIL-11 antibodies. Patients were women with stage II, III, or IV breast cancer undergoing dose-intensive chemotherapy with cyclophosphamide and doxorubicin.[U] Patients with a history of atrial arrhythmias or any condition known to increase the risk of atrial arrhythmias were excluded. Stratification was by investigator and previous chemotherapy (yes/no). The study required two blinded cycles without dose reduction or crossover. Neumega® could be given for up to four additional cycles for patients who continued to receive the same chemotherapy regimen without any dose reduction. Patients were randomized to:

Neumega® 50 μg/kg SQ QD Days 2 through 11/18[V]

—or—

Placebo SQ QD Days 2 through 11/18[V]

All patients received G-CSF 5 μg/kg SQ QD Day 2 until ANC ≥ 10,000/μL. Antiemetics were given prophylactically as per institutional practice (ondansetron and dexamethasone were recommended). Additional supportive care (*e.g.*, diuretics and electrolytes) were administered as needed. Ciprofloxacin 500 mg PO BID was given to all patients from Day 2 until ANC ≥ 1,000/μL. Prophylactic platelet transfusions were given for platelet counts ≤20,000/μL. RBC transfusions were given at the investigator's discretion. Daily platelet counts were obtained when the platelet count was <50,000/μL. Chemotherapy and all supportive care (including study drug and G-CSF) was repeated at 21- to 28-day intervals, pending recovery to WBC ≥3,000/μL and platelet count ≥ 100,000/μL.[W]

The primary endpoint was whether or not a patient required one or more platelet transfusions during two cycles of chemotherapy.[X] Safety was assessed in terms of the number of adverse events and abnormal laboratory test results. The number of RBC transfusions and tumor response information was also collected. Secondary endpoints included: time to ANC >500/μL; number of transfusions; duration of platelet count <50,000/μL; AUC of the rhIL-11 concentration time curve; and the presence of anti-rhIL-11 antibodies. All patients were to be evaluable except those who discontinued

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[U] CPA 3200 mg/m^2 & DOX 75 mg/m^2 IV on day 1.

[V] Study drug was discontinued on Day 11 if the platelet count was ≥50,000/μL and a platelet transfusion had not been given on either Day 9 or 10. If the platelet count on Day 11 was <50,000/μL or if a platelet transfusion was given on Day 9 or 10 study drug continued until Day 18.

[W] If the WBC or platelet count had not recovered by Day 22, or if any grade ≥3 non-hematologic toxicity had not resolved, treatment was delayed for 7 days. If the toxicity had not recovered by Day 29, the patient was discontinued from the study.

[X] Originally, the primary endpoint was the number of platelet transfusions. However, a planned interim analysis after ~⅓ of the patients had been enrolled showed the number of platelet transfusions was far less than had been predicted. The primary endpoint was changed by amendment in May 1995 while the study was still blinded.

THE STUDY BEFORE RECEIVING A FULL COURSE OF STUDY DRUG DUE TO EITHER CANCER PROGRESSION; TOXICITY UNRELATED TO STUDY DRUG; OR THOSE WITH A MAJOR PROTOCOL VIOLATION. HOWEVER, THOSE PATIENTS WHO RECEIVED PLATELET TRANSFUSION IN CYCLE 1 AND WHO DID NOT PROCEED TO CYCLE 2 WERE CONSIDERED EVALUABLE, SINCE THEY MET THE DEFINITION OF "FAILURES." IN ADDITION, AN INTENT-TO-TREAT ANALYSIS WAS TO BE PERFORMED ON ALL PATIENTS WHO RECEIVED AT LEAST ONE DAY OF STUDY DRUG, WHETHER OR NOT THEY COMPLETED THE TWO BLINDED CYCLES.

STUDY RESULTS—EFFICACY

SEVENTY-SEVEN PATIENTS WERE ENROLLED AND RANDOMIZED: 37 TO THE PLACEBO ARM AND 40 TO THE NEUMEGA® ARM. THE ARMS WERE BALANCED FOR AGE, RACE, MENOPAUSAL STATUS, STAGE OF DISEASE, AND PERFORMANCE SCORE. THE DEMOGRAPHICS ARE TABULATED BELOW.

TABLE Nº 28—STUDY C9416: PATIENT DEMOGRAPHICS

DEMOGRAPHIC CHARACTERISTIC		STUDY ARM		TOTAL
		PLACEBO N=37	NEUMEGA® N=40	
AGE (YEARS):	MEAN	45.7	47.9	*46.8*
	RANGE	25-75	36-63	*25-75*
RACE:	BLACK	6 (16%)	7 (17%)	*13 (17%)*
	CAUCASIAN	28 (76%)	32 (80%)	*60 (78%)*
	HISPANIC	2 (5%)	0	*2 (3%)*
	OTHER	1 (3%)	1 (3%)	*2 (3%)*
MENOPAUSAL STATUS:	PRE-	18 (49%)	19 (48%)	*37 (48%)*
	POST-	14 (38%)	18 (45%)	*32 (42%)*
	PERI-	5 (13%)	3 (7%)	*8 (10%)*
DISEASE STAGE:	2	7 (19%)	5 (12%)	*12 (16%)*
	3	12 (32%)	10 (25%)	*22 (29%)*
	4	18 (49%)	25 (63%)	*43 (56%)*
ECOG PERFORMANCE SCORE:	0	31 (84%)	31 (78%)	*62 (81%)*
	1	4 (11%)	7 (17%)	*11 (14%)*
	≥2	2 (5%)	2 (5%)	*4 (5%)*
PRIOR THERAPY:	YES	10 (27%)	13 (32%)	*23 (30%)*
	NO	27 (73%)	27 (68%)	*54 (70%)*

As with study C9308, the sponsor conducted a statistical analysis on three patient populations: an intent-to-treat (ITT) population, an evaluable subgroup (ESG) population, and a "completer" subgroup (CSG) population. The protocol for study C9416 stated the primary efficacy analysis was to be performed on the ESG population. The sponsor's analyses of the three populations were confirmed; however, exploratory analyses were only conducted on the ITT and ESG populations—for reasons previously discussed (see page 22, above).

All patients randomized received at least one dose of study drug. Thirteen patients (17%) dropped out of the study before Cycle 2—seven in the placebo arm and six in the Neumega® arm. The reasons are summarized below.

TABLE Nº 29—Study C9416: Patients Failing to Enter Cycle 2

Reason for Discontinuation	Study Arm		*Total*
	Placebo	Neumega®	
Adverse Event[Y]	2	4	6
Chemotherapy[Z]	3	1	4
Disease Progression	1	0	1
Withdrew Consent	1	0	1
Death	0	1	1
TOTALS	7	6	13

Of the 13 patients not entering Cycle 2, five (one in the placebo arm and four in the Neumega® arm) were transfused during Cycle 1. These five patients were considered evaluable since they had met the protocol definition of "failure" before they dropped out. Eight of the patients who did not enter Cycle 2 (six in the placebo arm and two in the Neumega® arm) were not transfused in Cycle 1 and, thus, were considered not evaluable. An additional two patients, who did complete Cycle 2, were also considered not evaluable because of major protocol evaluations.[AA] Therefore, the ESG population

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[Y] The adverse events responsible for discontinuation in the placebo arm were throat tightness and atrial fibrillation/flutter, each in one patient. In the Neumega® arm the adverse events were mucositis, dyspnea, atrial fibrillation/flutter, and diarrhea, also each in one patient.

[Z] According to the report, patients "*...classified as discontinuing because of chemotherapy discontinued the study because they did not wish to continue the specific chemotherapy regimen used in this study, although their discontinuation was not linked by the investigator to a specific adverse event.*"

[AA] Patient 033, randomized to placebo, missed four consecutive counts in Cycle 2 when her platelet count was <50,000/μL. She had 1 week of platelet counts in the 35-49,000/μL range before missing the four counts. Her next, and last, platelet count was 70,000/μL. This patient never had a platelet count ≤20,000/μL in either blinded cycle, and was not transfused. Patient 086, randomized to Neumega®, was not transfused in Cycle 2 when her platelet count was 20,000/μL. This was her only count ≤20,000/μL in either blinded cycle.

consisted of 67 patients: 30 in the placebo arm and 37 in the Neumega® arm. Since all patients randomized received study drug, the ITT population consisted of 77 patients: 37 in the placebo arm and 40 in the Neumega® arm.

According to the sponsor's ESG analysis, 40 patients avoided platelet transfusion over the two blinded cycles: 14 of 30 (47%) in the placebo arm and 26 of 37 (70%) in the Neumega® arm. This difference did not reach statistical significance (p=0.08 by Fisher's Exact Test). The ESG analysis does not include the two patients considered not evaluable because of a major protocol violation. In the protocol, a major violation was defined as one "*...that could confound the interpretation of the patient's outcome for the primary analysis.*" Although the protocol violations were certainly major, the outcome for each patient (as far as platelet transfusion goes) could be hypothesized, given the data available. The patient who missed four consecutive platelet counts almost certainly would not have required platelet transfusion, since the missed counts were 1 week post-nadir, and just prior to recovery. The patient not transfused with a platelet count of 20,000/μL should have been transfused. If these two patients are included in the ESG population, it would mean 15 out of 31 patients (48%) in the placebo arm avoided platelet transfusion compared to 26 out of 38 patients (68%) in the Neumega® arm (p=0.14 by Fisher's Exact Test).

For the ITT analysis, the patients who dropped out of Cycle 1 without being transfused needed to have an outcome assigned. For the ITT analysis, the sponsor considered them as treatment failures (*i.e.*, as having been transfused).[BB] With this outcome assignment, 15 of the 37 patients (41%) in the placebo arm avoided transfusion and 27 of the 40 patients (68%) in the Neumega® arm avoided transfusion. This difference was statistically significant (p=0.02 by Fisher's Exact Test). If the patient with the platelet count of 20,000/μL who was not transfused were to be included as having been transfused), the outcome is not significantly altered—it would mean that 41%of the patients in the placebo arm avoided transfusion *vs* 65% of the patients in the Neumega® arm (p=0.04 by Fisher's Exact Test).

As noted previously, one of the benefits of an ITT analysis is it is usually a conservative analysis, and assigning "failure" to patients for whom the outcome is unknown is often the most conservative approach. However, in this study there was a major imbalance in the numbers of patients in each arm needing outcome assignment—six in the placebo arm and two in the Neumega® arm. Thus, assigning "failure" to those patients with unknown outcomes would bias the study in favor of the study drug. Since the incidence of severe thrombocytopenia—and therefore platelet transfusion—was less than 50% it would be reasonable—and more conservative—to assign a favorable outcome (*i.e.*, avoidance of transfusion) to all patients for whom the outcome is unknown. Another alternative would be to proportion the assignments 50-50. The most conservative approach would be to consider the six patients in the placebo arm as "successes" and the two patients in the Neumega® arm as "failures" (the worst-case scenario). Because of the size of the study and the imbalance between the arms, the particular assignment of outcome significantly changes the results. The results of these exploratory analyses are presented in the

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[BB] This decision was not prospectively made in the study protocol. However, according to the study report, the decision was made after the study was completed, but prior to unblinding.

TABLE BELOW. FOR THESE EXPLORATORY ANALYSES, THE PATIENT WHO WAS NOT TRANSFUSED WITH A PLATELET COUNT 20,000/μL WAS CLASSIFIED AS HAVING BEEN TRANSFUSED.

TABLE Nº 30—STUDY C9416: OUTCOME ASSIGNMENT FOR ITT ANALYSIS

ASSIGNMENT OF OUTCOME	PLATELET TRANSFUSION	STUDY ARM		P-VALUE (FISHER'S EXACT)
		PLACEBO N=37	NEUMEGA® N=40	
UNKNOWN OUTCOME ASSIGNED AS PLATELET TRANSFUSION (FAILURE)	YES	22 (59%)	14 (35%)	0.04
	NO	15 (41%)	26 (65%)	
UNKNOWN OUTCOMES ASSIGNED HALF AS SUCCESS & HALF AS FAILURE	YES	19 (51%)	13 (32%)	0.11
	NO	18 (49%)	27 (68%)	
UNKNOWN OUTCOME ASSIGNED AS NO PLATELET TRANSFUSION (SUCCESS)	YES	16 (43%)	12 (30%)	0.25
	NO	21 (57%)	28 (70%)	
PLACEBO UNKNOWNS ASSIGNED AS SUCCESS & NEUMEGA® UNKNOWNS AS FAILURE	YES	16 (43%)	14 (35%)	0.49
	NO	21 (57%)	26 (65%)	

THE HOMOGENEITY OF THE TREATMENT EFFECT ACROSS CENTERS WAS INVESTIGATED. THERE WERE 14 INVESTIGATIVE SITES; HOWEVER, AS IN STUDY C9308, PATIENTS WERE NOT UNIFORMLY DISTRIBUTED. TWO SITES HAD 13 PATIENTS EACH, ONE SITE HAD NINE PATIENTS, TWO SITES HAD EIGHT PATIENTS EACH, THREE SITES HAD FIVE PATIENTS EACH, AND ONE SITE HAD THREE PATIENTS. THE REMAINING FIVE SITES ENROLLED ONE OR TWO PATIENTS EACH—AND ONLY ONE OF THESE SITES HAD A PATIENT IN EACH STUDY ARM. IN GENERAL, THE NUMBER OF PATIENTS RANDOMIZED TO EACH TREATMENT ARM WAS WELL-BALANCED IN EACH OF THE SITES. OF THE SITES WITH AT LEAST FIVE ENROLLED PATIENTS, ONE SITE SHOWED AN APPRECIABLE TREATMENT EFFECT.[CC] THE EFFECT IN THE OTHER SITES WAS MARGINAL; HOWEVER, HERE WAS NO SITE AT WHICH THE PLACEBO PATIENTS FARED BETTER THAN THE NEUMEGA® PATIENTS WITH RESPECT TO THE PRIMARY ENDPOINT. A TEST OF HOMOGENEITY OF TREATMENT EFFECT ACROSS THE CENTERS WAS PERFORMED USING *STATXACT*. THE P-VALUE WAS 0.77, WHICH DID NOT SUPPORT THE LACK OF HOMOGENEITY ACROSS CENTERS[DD] SUGGESTING THAT THE TREATMENT EFFECT WAS RELATIVELY HOMOGENEOUS.

PATIENTS WERE STRATIFIED AT RANDOMIZATION BY WHETHER OF NOT THEY HAD RECEIVED PREVIOUS CHEMOTHERAPY. ALTHOUGH THE NUMBER OF PATIENTS IN THE PRIOR CHEMOTHERAPY SUBGROUP WAS SMALL, THERE APPEARED TO BE A DIFFERENCE IN PLATELET TRANSFUSION BETWEEN THE PLACEBO ARM AND THE NEUMEGA® ARM. ONE OF TEN PATIENTS IN THE PLACEBO ARM (10%) AVOIDED PLATELET TRANSFUSION *VS* SEVEN OF 13 PATIENTS (54%) IN THE NEUMEGA® ARM (P=0.21 BY FISHER'S EXACT TEST). HOWEVER, THERE WAS LESS DIFFERENCE SEEN BETWEEN THE TWO TREATMENT GROUPS

[CC] ONE OF THREE PATIENTS IN THE PLACEBO ARM AVOIDED PLATELET TRANSFUSION *VS* FOUR OF FOUR PATIENTS IN THE NEUMEGA® ARM.

[DD] IT SHOULD BE NOTED THAT THE METHOD OF THIS ANALYSIS EXCLUDES SIX SITES, CONTRIBUTING 17 PATIENTS, BECAUSE OF ZEROS IN THE MARGINS OF TABLES.

IN THE NO PRIOR CHEMOTHERAPY SUBPOPULATION. FOURTEEN OF 27 PATIENTS (52%) IN THE PLACEBO ARM AVOIDED PLATELET TRANSFUSION *VS* 19 OF 27 PATIENTS (70%) IN THE NEUMEGA® ARM (P=0.77 BY FISHER'S EXACT TEST). ALTHOUGH THERE APPEARED TO BE A TREATMENT INTERACTION BY PRIOR CHEMOTHERAPY, A TEST FOR TREATMENT INTERACTION USING ZELEN'S STATISTIC (*STATXACT*) GAVE A P-VALUE OF 0.27. THESE ANALYSES ARE SUMMARIZED IN THE TABLE BELOW.

TABLE Nº 31—STUDY C9416: OUTCOME BY PRIOR CHEMOTHERAPY (ITT ANALYSIS)

PRIOR CHEMOTHERAPY	PLATELET TRANSFUSION	STUDY ARM		P-VALUE
		PLACEBO	NEUMEGA®	
NO (N=54)	YES	9 (33%)	7 (26%)	0.77
	NO	14 (52%)	19 (70%)	
	NOT EVALUABLE	4 (15%)	1 (4%)	
YES (N=23)	YES	7 (70%)	5 (38%)	0.21
	NO	1 (10%)	7 (54%)	
	NOT EVALUABLE	2 (20%)	1 (8%)	

SECONDARY ENDPOINTS INCLUDED THE TIME TO PLATELET RECOVERY AND THE NUMBER OF PLATELET AND RBC TRANSFUSIONS. LESS THAN HALF OF THE PATIENTS HAD PLATELET COUNTS ≤20,000/μL, AND THE MEDIAN TIME TO PLATELET COUNT ≥20,000/μL WAS 0 DAYS IN BOTH ARMS OF BOTH CYCLES. THERE WERE NO STATISTICALLY SIGNIFICANT DIFFERENCES IN THE NUMBER OF EITHER PLATELET OR RBC TRANSFUSIONS BETWEEN THE TWO ARMS. THESE DATA ARE TABULATED BELOW. HOWEVER, BECAUSE OF THE DIFFERENTIAL DROPOUT FROM CYCLE 1 TO CYCLE 2 (FOUR OF EIGHT PATIENTS (50%) IN THE NEUMEGA® ARM WHO WERE TRANSFUSED IN CYCLE 1 DROPPED OUT, WHEREAS SIX OF 27 PATIENTS IN THE PLACEBO ARM PATIENTS (22%) WHO WERE NOT TRANSFUSED IN CYCLE 1 DROPPED OUT) VALID COMPARISONS OF THE TWO ARMS CANNOT BE MADE FOR CYCLE 2.

TABLE Nº 32—STUDY C9416: PLATELET TRANSFUSIONS

NUMBER OF TRANSFUSION EVENTS		STUDY CYCLE & ARM			
		STUDY CYCLE 1		STUDY CYCLE 2	
		PLACEBO N=37	NEUMEGA® N=40	PLACEBO N=30	NEUMEGA® N=34
PLATELET TRANSFUSIONS:	MEDIAN	0	0	0	0
	MEAN	0.4	0.3	1.5	0.3
	RANGE	0-6	0-4	0-11	0-3
RBC TRANSFUSIONS:	MEDIAN	0	0	0	1.0
	MEAN	0.3	0.5	0.6	0.7
	RANGE	0-3	0-3	0-3	0-2

Study Results—Safety

All 77 patients randomized received at least one dose of study drug and were evaluable for the safety analysis. The number of patients reporting adverse events was similar in Cycles 1 and 2 and the data from both cycles were combined for analysis. Treatment with Neumega® was generally well-tolerated. Four adverse events were associated with Neumega® ($p < 0.05$ by Fisher's Exact Test) during Cycles 1 and 2: edema, dyspnea, pleural effusion, and conjunctival injection. The incidence and severity of these side effects is given below;

TABLE Nº 33—Study C9416: Adverse Events in Cycles 1 & 2

Adverse Event	Study Arm			
	Placebo (N=37)		Neumega® (N=40)	
	Total	Grade ≥3	Total	Grade ≥3
Edema	5 (14%)	0	25 (62%)	3 (8%)
Dyspnea	7 (19%)	0	19 (48%)	4 (10%)
Conjunctival Injection	0	0	10 (25%)	0
Pleural Effusion	0	0	7 (18%)	3 (8%)

The incidence of edema was similar to that reported in study C9206 (77%), the phase 1 trial in adults. As in that study, most (92%) were mild to moderate. Six of the patients with dyspnea in the Neumega® arm also had pleural effusions. All pleural effusions occurred in patients with stage IV disease. One of the patients with pleural effusion died suddenly of a cardiopulmonary arrest on Day 6 of Neumega®. The conjunctival injection reported in the patients receiving Neumega® was a redness not associated with tearing or itching. Other adverse events possibly associated with Neumega® ($p<0.1$, but $p>0.05$) were allergic reaction, dehydration, exfoliative dermatitis, flu syndrome, increased cough, left heart failure, oral moniliasis, sinusitis, and skin discoloration. In contradistinction to study C9308, anemia, anorexia, atrial arrhythmias, fever, headache, palpitations, and tachycardia were not associated with Neumega® in study C9416.[EE]

Fourteen patients dropped out of the study because of an adverse event: five in the placebo arm and nine in the Neumega® arm. One patient in each arm discontinued because of atrial fibrillation/flutter. Both were judged to be "possibly" related to study drug. One patient in the placebo arm discontinued because of a skin reaction judged to be "definitely" related to study drug. Another patient in the placebo arm dropped out because of facial flushing judged to be "possibly" related. One patient in the Neumega® arm discontinued because of two adverse events (edema, judged to be "probably" related, and arthralgias, considered to be "possibly" related). Another patient in the Neumega® arm dropped out because of papilledema, judged to be "definitely" related to

[EE] It should be remembered that patients with a prior history of atrial arrhythmias or conditions known to increase the risk of atrial arrhythmias were excluded from this study.

study drug. All other AEs resulting in discontinuation were judged to be not related or of unknown relationship to study drug.[FF]

As in study C9308, Hgb concentrations dropped in both study arms. The drops were of similar magnitude from baseline, and again occurred earlier in the Neumega® arm. In the placebo arm the drop from baseline was 16% in Cycle 1 and 12% in Cycle 2. In the Neumega® arm the drop from baseline was 18% in Cycle 1 and 13% in Cycle 2. However, in contradistinction to study C9308, neither arm completely returned to baseline. The Hgb data are summarized below.

TABLE Nº 34—Study C9416: Mean Hgb Concentrations

Cycle Number	Study Arm	Mean Hgb Concentration (g/dL) on Study Day						
		0	2	4	7	14	20	26
1	Placebo	11.7	11.2	11.7	10.4	9.8	10.3	NA
	Neumega®	11.6	10.9	10.8	9.5	9.8	9.8	10.1
2	Placebo	10.6	10.3	10.5	9.9	9.3	10.0	9.5
	Neumega®	10.5	9.8	9.9	9.1	9.7	9.8	10.2

There was no evidence of an adverse effect on neutrophil recovery—or an adverse drug interaction with G-CSF. All patients recovered, and recovery was similar in both arms for the two blinded cycles. For their analysis, FDA dated recovery from the initiation of chemotherapy, instead of study drug. Also, missing data were handled somewhat differently. The data on neutrophil recovery are presented in the table below.

TABLE Nº 35—Study C9416: Neutrophil Recovery

Analysis		Days to ANC ≥500/μL							
		Cycle 1				Cycle 2			
		N	Placebo	N	Neumega®	N	Placebo	N	Neumega®
Sponsor:	Median	37	11.0	40	10.5	30	10.0	34	10.5
	95% CI		11.0-12.0		9.0-11.0		0-12.0		0-12.0
FDA:	Median	37	13.0	39	12.0	30	12.5	34	12.0
	Mean		13.0		12.3		12.6		12.4
	Range		11-20		0-16		0-17		11-15

[FF] These were renal insufficiency and throat tightness in the placebo arm and aortic stenosis, decreased ejection fraction, diarrhea, dyspnea, mucositis, and neutropenic fever in the Neumega® arm.

Four patients died while on study, and three patients died after completion of the study. Except for the patient (described above) who died of a cardiopulmonary arrest, all died of progression and/or a complication of their disease.

Overall, 59 patients had some degree of exposure to Neumega®, including those crossed-over in the open-label cycles. Conclusions regarding antibody formation could not be drawn for patients who received only one dose or whose sampling was not sufficient to permit detection of an antibody response. Antibody formation was able to be assessed in 45 of the 59 patients. All samples were negative in the antibody ELISA.

VI. TRIALS IN THE POST-MYELOABLATIVE CHEMOTHERAPY SETTING

Background

Over 100 patients have been enrolled in clinical trials of Neumega® after myeloablative chemotherapy. Studies C9301 and C9313 have been completed, and these two trials will be reviewed briefly. Study C9525 has just been initiated, and data are available on only one patient. It will not be reviewed. Since the proposed indication for Neumega® does not include its use after myeloablative chemotherapy, the data were submitted primarily for safety.

Study C9301—Phase 1/2 Trial

Study C9301 "*Phase 1/2 study of recombinant human interleukin 11 (NEUMEGA™ rhIL-11 growth factor) following autologous bone marrow transplantation in patients with high-risk breast cancer*" was initiated in August 1993 and completed in September 1994. It was an open-label, nonrandomized, uncontrolled, single-center, dose-escalating phase 1/2 study. The primary objective was to evaluate the safety of Neumega® in patients with high-risk breast cancer undergoing AuBMT. Doses of 10, 25, 50, 75, and 100 µg/kg/d SQ x28 days were to be studied in cohorts of three patients. All patients received the same preparative chemotherapy[GG] on days -7, -6, and -5 with bone marrow infusion, Neumega®, and concomitant G-CSF starting on day 0. Since there was no "Cycle 0", adverse reaction reporting was confounded by chemotherapy.

A total of 21 patients were enrolled. One additional patient was studied at the 25 µg/kg dose; three additional patients were studied at the 50 µg/kg dose; and five patients were studied at the 75 µg/kg dose. Dose escalation was not continued beyond 75 µg/kg due to the incidence and severity of significant cardiovascular or pulmonary adverse events. Six patients dropped out of the study: one withdrew consent and five due to an adverse event (AE). The one patient who withdrew consent did so after receiving two doses of Neumega®. This patient was experiencing multiple adverse events (esophagitis, mucositis, dysphagia, *etc*), none of which were judged to be related to Neumega®. The adverse events leading to discontinuation from the study, and the investigator's judgement of causality, are summarized on the following page.

[GG] CPA 2 g/m^2 IV; BCNU 150 mg/m^2 IV; & thiotepa 240 mg/m^2 IV.

TABLE Nº 36—STUDY C9301: ADVERSE EVENTS LEADING TO DISCONTINUATION

PATIENT Nº	DOSE (µG/KG/D)	ADVERSE EVENT RESULTING IN STUDY DRUG DISCONTINUATION	CAUSALITY AS JUDGED BY PI
021	50	ATRIAL FIBRILLATION	PROBABLY RELATED
012	75	EDEMA, CONGESTIVE HEART FAILURE	POSSIBLY RELATED
014	75	RESPIRATORY FAILURE	POSSIBLY RELATED
016	75	PULMONARY EDEMA	UNKNOWN
018	75	ATRIAL FLUTTER	PROBABLY RELATED

MILD TO MODERATE ADVERSE EVENTS WERE REPORTED BY ALL PATIENTS. THE MOST FREQUENTLY REPORTED ADVERSE EVENTS WERE NEUTROPENIC FEVER (21 PATIENTS); DIARRHEA (20 PATIENTS); EDEMA AND STOMATITIS (19 PATIENTS); FEVER, INCREASED COUGH, AND RHINITIS (18 PATIENTS); ASTHENIA AND RASH (17 PATIENTS); DYSPNEA (16 PATIENTS); HYPERVOLEMIA (15 PATIENTS); CHILLS (14 PATIENTS); ANOREXIA (13 PATIENTS); ABDOMINAL PAIN AND TACHYCARDIA (11 PATIENTS); AND EYE HEMORRHAGE AND PNEUMONIA (10 PATIENTS).

NINE PATIENTS (43%) EXPERIENCED AT LEAST ONE CARDIOVASCULAR ADVERSE EVENT: SIXTEEN EVENTS WERE REPORTED IN THE NINE PATIENTS. THE INVESTIGATOR JUDGED EIGHT OF THE 16 EVENTS (50%) TO BE POSSIBLY RELATED TO STUDY DRUG TREATMENT. A COMPLETE LIST OF PATIENTS AND CARDIAC EVENTS IS TABULATED BELOW.

TABLE Nº 37—STUDY C9301: CARDIAC ADVERSE EVENTS

PATIENT Nº	DOSE (µG/KG/D)	CARDIAC ADVERSE EVENT	CAUSALITY AS JUDGED BY PI
006	25	CONGESTIVE HEART FAILURE (2 EVENTS)	UNKNOWN
		CARDIOMYOPATHY	NOT RELATED
009	50	ATRIAL FLUTTER	NOT RELATED
		CONGESTIVE HEART FAILURE	UNKNOWN
019	50	CONGESTIVE HEART FAILURE	NOT RELATED
020	50	CONGESTIVE HEART FAILURE	NOT RELATED
021	50	ATRIAL FIBRILLATION	PROBABLY RELATED
011	75	ATRIAL FIBRILLATION (2 EVENTS)	POSSIBLY RELATED
012	75	CONGESTIVE HEART FAILURE	POSSIBLY RELATED
013	75	ATRIAL FIBRILLATION (2 EVENTS)	POSSIBLY RELATED
018	75	CONGESTIVE HEART FAILURE	NOT RELATED
		ATRIAL FIBRILLATION/FLUTTER (2 EVENTS)	PROBABLY RELATED

Fifteen of the 21 patients (71%) reported at least one grade ≥3 adverse event. A total of 41 grade ≥3 events were reported in the 15 patients—24 (58%) occurred at the 75 μg/kg dose level. Five of these were cardiovascular adverse events. Grade ≥3 AEs occurred at all doses studied. The grade ≥3 AEs reported in more than one patient were: neutropenic fever (5), congestive heart failure (4), esophagitis (3), stomatitis (3), hypotension (2), hypervolemia (2), and lung edema (2). Twenty-eight of the 41 grade ≥3 AEs (68%) were judged to be not related to study drug by the investigator. Four were judged to be at least possibly related: These were pulmonary edema, congestive heart failure, and hypotension—all of which occurred in the same patient—and respiratory failure. The remaining nine were judged to be of unknown relationship: They were neutropenic fever (3), congestive heart failure (2), left ventricular dysfunction (1), cyanosis (1), and fluid overload (1).

Patients had frequent evaluations of hematology and chemistry parameters. All changes in the hematology parameters were expected, and not judged associated with Neumega®. No significant changes in PT and PTT were observed, nor were there any significant changes in mean sodium, potassium, chloride, or bicarbonate levels. There were no clinically significant changes in mean creatinine levels. Albumin decreased in all dosing groups. The mean percent change in albumin for all doses was -9.4% ± 2.8%. Calcium values decreased in all patients and at all doses studied. For all doses administered, the decrease in calcium ranged from -5.8% ± 1.6% at 75 μg/kg to -10.5% ± 3.2% at 10 μg/kg. By Day 28 nearly all patients had returned to baseline levels. If adjustments for hypoalbuminemia are made, the concentrations of unbound calcium generally fell within the normal range. Fibrinogen levels increased at all dose levels. Fibrinogen levels increased during the first week, remained elevated, began to decrease during the third week of dosing, but had not returned to baseline by Day 28. Changes in mean levels of C-reactive protein were also observed at all doses studied. Mean values of C-reactive protein increased dramatically by Day 14 of Neumega® administration. The percentage change from baseline to Day 14 ranged from almost 2,000% for the 25 μg/kg dose group to almost 3,000% for the 50 μg/kg dose group. C-reactive protein remained elevated at 28 days of dosing. Of the 17 patients for whom antibody formation could be evaluated, none demonstrated antibody formation to rhIL-11.

One patient, who received 9 days of Neumega® 75 μg/kg, died more than 14 days after discontinuing Neumega®. This patient had sepsis—complicated by bilateral pneumonia and respiratory failure requiring mechanical ventilation—and died of multiorgan failure. The investigator judged the patient's respiratory failure possibly related to study drug. All other AEs were judged to be unrelated or of unknown relationship to study drug.

Study 9313—Phase 2 Trial in AuBMT

Study 9313 "*Phase II study of recombinant human interleukin eleven (NEUMEGA® rhIL-11 growth factor) at doses of 25 and 50 μg/kg/d vs placebo following autologous bone marrow transplantation (ABMT) with peripheral blood progenitor support in patients with high-risk breast cancer*" was initiated in March 1994 and completed in February 1996. It was a single-center, randomized, double-blind, placebo-controlled phase 2 study of placebo and two doses of Neumega® in women with high-risk breast cancer who were

UNDERGOING HIGH-DOSE CHEMOTHERAPY WITH AUTOLOGOUS BONE MARROW TRANSPLANTATION AND PERIPHERAL BLOOD PROGENITOR SUPPORT. PATIENTS WITH "*...HISTORIES OF ATRIAL FIBRILLATION OR CONDITIONS KNOWN TO PREDISPOSE TO ATRIAL FIBRILLATION...*" WERE EXCLUDED.

ALL PATIENTS RECEIVED THE SAME PREPARATIVE REGIMEN[HH] STARTING ON DAY -6 AND CONTINUING THROUGH DAY -3. ON DAY -2 PATIENTS WERE STRATIFIED BY STAGE OF DISEASE (II/III *VS* IV), AND RANDOMIZED TO: NEUMEGA® 25 µG/KG, NEUMEGA® 50 µG/KG, OR PLACEBO.[II] ON DAYS -1, 0, AND 1 ALL PATIENTS RECEIVED PERIPHERAL BLOOD PROGENITOR CELLS, EACH INFUSION CONTAINING 1×10^{10} MONONUCLEAR CELLS (MNC). STUDY DRUG AND CONCOMITANT G-CSF WERE STARTED ON DAY -1. ON DAY 1 PATIENTS RECEIVED AUTOLOGOUS BONE MARROW, CONTAINING 1×10^{8} MNC/KG.

THE PRIMARY STUDY OBJECTIVES WERE TO COMPARE THE ACTIVITY AND SAFETY OF THE TWO DOSES OF NEUMEGA® WITH PLACEBO IN STIMULATING HEMATOLOGIC RECOVERY. SECONDARY OBJECTIVES INCLUDED THE MEASUREMENT OF SERUM RHIL-11 LEVELS, ANTI-RHIL-11 ANTIBODY PRODUCTION, AND PLATELET RETICULOCYTES.

A TOTAL OF 80 WOMEN WERE RANDOMIZED: 26 TO PLACEBO, 28 TO NEUMEGA® 25 µG/KG, AND 26 TO NEUMEGA® 50 µG/KG. THEIR DEMOGRAPHIC CHARACTERISTICS ARE SUMMARIZED BELOW.

TABLE Nº 38—STUDY 9313: DEMOGRAPHIC CHARACTERISTICS

DEMOGRAPHIC CHARACTERISTIC		STUDY ARM			OVERALL N=80
		PLACEBO N=26	NEUMEGA® 25 µG/KG N=28	NEUMEGA® 50 µG/KG N=26	
AGE (YEARS):	MEAN	44.1	43.0	42.5	43.2
	RANGE	31-68	30-55	35-51	30-68
RACE:	BLACK	4 (15%)	2 (7%)	5 (19%)	11 (14%)
	WHITE	22 (85%)	24 (86%)	21 (81%)	67 (84%)
	OTHER	0	2 (7%)	0	2 (2%)
MENOPAUSAL STATUS:	PRE	15 (58%)	14 (50%)	17 (65%)	46 (58%)
	POST	11 (42%)	14 (50%)	9 (35%)	34 (42%)
DISEASE STAGE:	II/III	8 (31%)	11 (39%)	9 (35%)	28 (35%)
	IV	18 (69%)	17 (61%)	17 (65%)	52 (65%)
ECOG SCORE:	0	12 (46%)	16 (57%)	18 (69%)	46 (58%)
	1	14 (54%)	12 (43%)	8 (31%)	34 (42%)

[HH] CPA 1875 MG/M² IV & CDDP 55 MG/M² CIV ON DAYS -6, -5, & -4 & BCNU 600 MG/M² IV ON DAY -3.

[II] AS IN STUDY C9308, PATIENTS RANDOMIZED TO PLACEBO UNDERWENT A SECOND RANDOMIZATION TO THE TWO VOLUMES OF PLACEBO EQUIVALENT TO THE TWO VOLUMES OF NEUMEGA®.

A TOTAL OF 18 PATIENTS (22%) FAILED TO COMPLETE THE STUDY. THEY WERE EQUALLY DISTRIBUTED AMONG THE THREE ARMS. FIVE PATIENTS WITHDREW CONSENT PRIOR TO RECEIVING STUDY DRUG, AND ONE WITHDREW CONSENT AFTER TWO DOSES OF NEUMEGA® 25 µG/KG. ELEVEN PATIENTS WITHDREW DUE TO AN ADVERSE EVENT—SIX BECAUSE OF ATRIAL FIBRILLATION/FLUTTER: ONE IN THE PLACEBO ARM, TWO IN THE 25 µG/KG ARM, AND THREE IN THE 50 µG/KG ARM. ALL WERE JUDGED TO BE "POSSIBLY RELATED" TO THE STUDY DRUG BY THE INVESTIGATOR. TWO PATIENTS WITHDREW BECAUSE OF VENO-OCCLUSIVE LIVER DISEASE, ONE EACH IN THE PLACEBO AND 25 µG/KG ARMS. OTHER REASONS FOR WITHDRAWAL WERE MYALGIAS, AN INCREASED ALKALINE PHOSPHATASE, AND AN EPISODE OF VENTRICULAR PAUSE ON HOLTER MONITOR WHICH OCCURRED PRIOR TO RECEIVING STUDY DRUG BUT WAS NOT RECOGNIZED UNTIL AFTER STUDY DRUG ADMINISTRATION HAD BEGUN. ONE PATIENT DIED OF PULMONARY TOXICITY ASSOCIATED WITH HIGH-DOSE CHEMOTHERAPY 18 DAYS AFTER COMPLETION OF STUDY DRUG. THE REASONS FOR DISCONTINUATION ARE SUMMARIZED BELOW.

TABLE Nº 39—STUDY 9313: DROPOUTS

REASON FOR FAILURE TO COMPLETE STUDY	STUDY ARM		
	PLACEBO N=26	NEUMEGA® 25 µG/KG N=28	NEUMEGA® 50 µG/KG N=26
WITHDREW CONSENT: BEFORE STUDY	1	2	2
DURING STUDY	0	1	0
ADVERSE EVENT	3	3	5
DIED	1	0	0
TOTAL	*5*	*6*	*7*

SEVENTY-FIVE PATIENTS RECEIVED AT LEAST ONE DOSE OF STUDY DRUG, AND ARE INCLUDED IN THE SAFETY ANALYSIS. AS IN STUDIES C9308 AND C9416, EDEMA WAS STATISTICALLY ASSOCIATED WITH NEUMEGA®. FIVE PATIENTS (20%) IN THE PLACEBO ARM DEVELOPED EDEMA COMPARED WITH 12 (46%) IN THE 25 µG/KG ARM AND 11 (46%) IN THE 50 µG/KG ARM (P=0.04 FOR THE PLACEBO ARM *VERSUS* THE COMBINED NEUMEGA® ARMS). AS IN STUDY C9416, CONJUNCTIVAL BLEEDING WAS REPORTED MORE FREQUENTLY IN THE NEUMEGA® ARMS. THERE WERE TWO REPORTS IN THE PLACEBO ARM (8%), FIVE REPORTS IN THE 25 µG/KG ARM (19%), AND TEN REPORTS IN THE 50 µG/KG ARM (P=0.04 FOR THE PLACEBO ARM *VERSUS* THE COMBINED NEUMEGA® ARMS). NONE OF THE CONJUNCTIVAL BLEEDING EPISODES IN THE PLACEBO ARM WAS ASSOCIATED WITH SEVERE THROMBOCYTOPENIA, WHEREAS THREE OF FIVE EPISODES IN THE 25 µG/KG ARM AND EIGHT OF TEN EPISODES IN THE 50 µG/KG ARM WERE ASSOCIATED WITH A PLATELET COUNT <20,000/µL.

STATISTICALLY SIGNIFICANT ASSOCIATIONS WERE ALSO FOUND BETWEEN THE 50 µG/KG ARM AND THE PLACEBO ARM FOR TACHYCARDIA (P=0.02) AND HYPOTENSION (P=0.02). TACHYCARDIA INCLUDED ALL ADVERSE EVENT REPORTS OF RAPID HEART RATE. SPECIFIC ARRHYTHMIAS WERE CLASSIFIED AS SUCH. ATRIAL FIBRILLATION/FLUTTER WAS REPORTED IN TWO PATIENTS (8%) IN THE PLACEBO ARM, TWO PATIENTS IN THE 25 µG/KG ARM, AND FIVE PATIENTS IN THE 50 µG/KG ARM. OF THE SEVEN NEUMEGA® PATIENTS WHO HAD ATRIAL ARRHYTHMIAS, FOUR RESULTED IN HOSPITALIZATION AND THREE WERE DETECTED ONLY BY EKG OR HOLTER MONITORING. TWO OF THESE THREE DID NOT RECEIVE ANY

antiarrhythmic treatment. Holter monitoring was performed on 43 patients: 14 in the placebo arm, 15 in the 25 μg/kg arm, and 14 in the 50 μg/kg arm. The monitoring was usually performed on the first 3 days of study drug administration and subsequently on 2 subsequent days at 1 week intervals. The results were analyzed by a consulting cardiologist, who found: [1] no significant changes in heart rate were associated with Neumega®; [2] no significant changes in ventricular ectopy were associated with Neumega®; [3] no significant pauses or bradycardia occurred in association with Neumega®; and [4] increased atrial ectopy was observed in 8 patients—4 in the placebo arm, 3 in the 25 μg/kg arm, and one in the 50 μg/kg arm. No arrhythmia-related symptoms were reported during the time the Holter monitor was recording the arrhythmias.

There were no clinically significant differences among the arms with respect to clinical chemistries, pO_2 saturation, chest X-rays, or thyroid function studies. The number of patients reporting grade ≥3 adverse events—including laboratory abnormalities—was small and evenly distributed across the arms. No specific grade ≥3 AEs were statistically associated with Neumega® (*i.e.*, $p<0.05$, by Fisher's exact test).

Significant hematologic toxicity following the myeloablative chemotherapy was universal. There was no difference in the time to neutrophil recovery, the time to platelet recovery, or the number of platelet or RBC transfusions between patients who received placebo and patients who received Neumega®. These data are tabulated below.

TABLE Nº 40—Study 9313: Hematologic Toxicity

Parameter		Study Drug		
		Placebo N=25	Neumega® 25 μg/kg N=26	Neumega® 50 μg/kg N=24
Days to ANC ≥500/μL:	Median	11	11	11
	Range	10-31	10-13	9-14
	Number Not Recovering	0	0	0
Days to Platelet Count ≥20,000/μL:	Median	15	14	17
	Range	12-83	11-47	11-48
	Number Not Recovering	3	1	0
Platelet Transfusions/Patient:	Median	8	7	9
	Mean±SD	11.4±10.2	8.0±4.6	8.8±3.5
	Range	3-46	3-22	4-17
RBC Units Transfused:	Median	2	3	4
	Mean±SD	3.0±2.7	2.9±1.6	3.4±1.6
	Range	0-12	0-6	0-6

Antibody formation was assessed in 68 patients who had received multiple doses of Neumega® or placebo and had sampling sufficient to detect an antibody response. None were found to have an antibody response to the rhIL-11 protein by ELISA.

VII. Effect of Neumega® on Tumor Progression

Background

In preclinical studies, rhIL-11 promoted the growth of some cell lines derived from tumors of megakaryoblastic origin. There was no other evidence of tumor stimulation.

- rhIL-11 failed to stimulate clonogenic growth of tumor cells in *in vitro* colony forming unit assays from any of 66 human tumor cultures—including lung, melanoma, ovary, prostate, stomach, brain, and breast tumors.
- rhIL-11 had no effect on the proliferation of three human melanoma cell lines derived from primary lesions or four lines derived from metastatic tumors.
- rhIL-11 did not alter the growth in culture of human colonic carcinoma cell lines.
- rhIL-11 had either no effect or minor and inconsistent effects on the growth of myeloma cells.

However, because Neumega® acts as a hematopoietic growth factor, there remains a theoretical possibility that it could stimulate a patient's underlying malignancy.

Tumor Response in the Controlled Trials

The three controlled trials were initially intended as phase 2 trials for a hematopoietic growth factor and, as such, were not optimally designed to monitor tumor response or the possibility of tumor stimulation. Not all patients enrolled had measurable disease. The sponsor considered 194 of the 240 patients who received at least one dose of study drug (81%) evaluable for tumor progression. The criteria used to determine evaluability were not given. These data are summarized below.

TABLE Nº 41—Effect of Neumega® on Tumor Progression

Study Nº	Study Arm					
	Placebo		Neumega® 25 µg/kg		Neumega® 50 µg/kg	
	Number Evaluable	Number with Progression	Number Evaluable	Number with Progression	Number Evaluable	Number with Progression
C9308	26	7 (27%)	26	10 (38%)	25	8 (32%)
C9313	23	0 (0%)	26	2 (8%)	24	1 (4%)
C9416	19	2 (11%)	—	—	25	4 (16%)

Thus, overall, nine of 68 evaluable patients (13%)—or 92 total patients (10%)—who received placebo had evidence of disease progression on study compared with 25 of 126 evaluable patients (20%)—or 148 total patients (17%)—who received Neumega®. These differences were not statistically significant (p=0.32 and 0.13, respectively).

A long-term follow-up registry was initiated to follow the course of patients treated with placebo or Neumega® in the three randomized, placebo-controlled clinical studies. Data were obtained by sending the investigative sites a case report form to complete with information about each patient's current status. Because of the heterogeneity of the population studied, precise criteria for following patients for disease progression were not specified. No specific tests or schedule of follow-up were required. The registry will be updated every 4-6 months for a period of 3 years from the date of the patient's first dose of study drug.

Data have been obtained on 238 of the 240 patients who received at least one dose of study drug:[JJ] 92 patients randomized to receive placebo and 146 patients randomized to receive Neumega®. Placebo patients who crossed-over to Neumega® in the open-label cycles were analyzed according to their randomized treatment assignment. Kaplan-Meier curves were constructed for overall and progression-free survival.

There was no statistically significant difference in either overall or progression-free survival between patients who received placebo and patients who received Neumega® in the three randomized studies. The median overall survival was 805 days and 755 days, respectively, and the median progression-free survival was 378 days and 296 days, respectively. These data are tabulated below.

TABLE Nº 42—Long-Term Survival in All Randomized Studies

Parameter		Study Drug		p-Value (log-Rank)
		Placebo N=92	Neumega® N=146	
Overall Survival (Days):	Median	805	755	0.44
	95% CI	505-	520-1023	
Progression-Free Survival (Days):	Median	378	296	0.59
	95% CI	255-612	220-482	

The results are similar for a comparison of placebo and Neumega® 50 µg/kg in the two pivotal trials (C9308 and C9416). The median overall survival was also 805 days and 755 days, and the median progression-free survival was 355 days and 426 days, respectively. These data are tabulated on the following page.

[JJ] One patient in study C9308—randomized to Neumega® 25 µg/kg—and one patient in study C9416—randomized to Neumega® 50 µg/kg—were lost to follow-up after completing their respective studies without disease progression.

TABLE Nº 43—LONG-TERM SURVIVAL IN STUDIES C9308 & C9416 (COMBINED)

PARAMETER		STUDY DRUG		P-VALUE (LOG-RANK)
		PLACEBO N=67	NEUMEGA® N=68	
OVERALL SURVIVAL (DAYS):	MEDIAN	805	755	0.67
	95% CI	477-	444-1023	
PROGRESSION-FREE SURVIVAL (DAYS):	MEDIAN	355	426	0.94
	95% CI	228-723	235-	

VIII. SUMMARY

GENERAL

TWO RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED TRIALS—C9308 AND C9416—WERE SUBMITTED TO SUPPORT THE EFFECTIVENESS OF NEUMEGA® IN PREVENTING THE NEED FOR PLATELET TRANSFUSION. THE TWO STUDIES DIFFERED IN DESIGN: C9308 STUDIED NEUMEGA® FOR SECONDARY PROPHYLAXIS FOLLOWING A PRIOR EPISODE OF SEVERE THROMBOCYTOPENIA; WHEREAS, C9416 STUDIED NEUMEGA® FOR PRIMARY PROPHYLAXIS STARTING WITH THE FIRST CYCLE OF CHEMOTHERAPY. THE PRIMARY ENDPOINT FOR BOTH OF THE STUDIES WAS THE NEED FOR PLATELET TRANSFUSION. THE STUDIES WERE DESIGNED AS PHASE 2 TRIALS AND, AS A RESULT, CONTAINED SOME MINOR DESIGN DEFICIENCIES. THE PRIMARY ANALYSIS FOR BOTH STUDIES WAS TO BE PERFORMED ON AN "EVALUABLE SUBGROUP" (ESG), RATHER THAN ON AN INTENT-TO-TREAT (ITT) BASIS, ALTHOUGH THE PROTOCOL DID STATE AN ITT ANALYSIS WOULD ALSO BE PERFORMED. THE STUDY PROTOCOLS DID NOT PROSPECTIVELY IDENTIFY HOW PATIENTS WHO FAILED TO COMPLETE THE STUDIES WOULD BE ANALYZED. THESE DECISIONS WERE MADE, HOWEVER, BEFORE UNBLINDING THE STUDIES. THE STUDIES WERE NOT DESIGNED TO OBTAIN DATA ON LONG-TERM DISEASE OUTCOME, ALTHOUGH A LONG-TERM FOLLOW-UP REGISTRY INITIATED AFTER THE STUDIES WERE CLOSED WAS ABLE TO OBTAINED DATA ON 163 OF THE 165 (99%) OF THE PATIENTS WHO RECEIVED STUDY DRUG IN THE TWO TRIALS. THESE DEFICIENCIES WERE RELATIVELY MINOR, AND OVERALL THE STUDY DESIGN AND CONDUCT WERE EXCELLENT—AND THE TWO TRIALS WOULD DEFINITELY SATISFY THE STATUTORY REQUIREMENT FOR "ADEQUATE AND WELL-CONTROLLED STUDIES" AS DEFINED IN 21 CFR § 314.126.

EFFECTIVENESS

OF THE TWO TRIALS, ONLY C9308 CONSISTENTLY STATISTICALLY DIFFERENTIATED NEUMEGA® FROM PLACEBO WITH REGARD TO THE PRIMARY ENDPOINT—A REDUCTION IN THE NEED FOR PLATELET TRANSFUSION. ACCORDING TO THE SPONSOR'S ITT ANALYSIS[KK] OF ALL PATIENTS RANDOMIZED, 93% OF THE PATIENTS IN THE PLACEBO ARM REQUIRED AT LEAST ONE PLATELET TRANSFUSION, COMPARED TO 81% OF THE PATIENTS IN THE 25 µG/KG ARM AND 62% OF THE PATIENTS IN THE 50 µG/KG ARM.

[KK] ALTHOUGH THE STUDY PROTOCOLS IDENTIFIED THE ESG ANALYSIS AS THE PRIMARY ANALYSIS AND THE ITT ANALYSIS AS A SECONDARY ANALYSIS, THIS WAS IN THE CONTEXT OF THE TRIALS AS PHASE 2 TRIALS. FOR PHASE 3 TRIALS THE ITT ANALYSIS IS PREFERRED, AND THE ITT ANALYSIS WILL SERVE AS THE "PRIMARY" ANALYSIS FOR THE PURPOSE OF THIS DISCUSSION.

The difference between placebo and Neumega® 50 μg/kg was statistically significant ($p<0.01$), whether or not an adjustment was made for multiplicity. According to the sponsor's ESG analysis, 96% of the patients in the placebo arm required at least one platelet transfusion, compared to 82% of the patients in the 25 μg/kg arm and 70% of the patients in the 50 μg/kg arm. Again, the difference between placebo and Neumega® 50 μg/kg was statistically significant ($p<0.05$), whether or not an adjustment was made for multiplicity. Several exploratory analyses were performed by FDA on both the ITT and ESG populations, retrospectively reclassifying patients and/or using alternative methods of handling missing data. These analyses also statistically differentiated placebo from Neumega® 50 μg/kg, consistently resulting in unadjusted p-values ≤0.05—with the exception of one analysis which resulted in a "borderline" p-value of 0.08. Thus, the FDA's exploratory analyses of study C9308 would also support the conclusion that a treatment effect was demonstrated.

The sponsor performed several exploratory subset analyses on the ESG population in study C9308. Neither age nor sex had a significant influence on outcome. The sponsor's analyses suggested patients with less prior therapy or shorter chemotherapy regimens were more likely to avoid platelet transfusion. None of the chemotherapy regimens was used frequently enough to allow reliable subset analyses, although only one of ~30 patients receiving one of two highly myelosuppressive regimens—DiCEP or ICE—avoided platelet transfusion. This observation suggested the treatment effect demonstrated in study C9308 might be limited to less highly myelosuppressive regimens. FDA performed an exploratory analysis using the time to ANC ≥500/μL as an indicator of the degree of myelosuppression. In patients who received a regimen which resulted in a time to ANC ≥500/μL of ≤10 days, 87% of the patients in the placebo arm required at least one platelet transfusion, compared to 67% of the patients in the 25 μg/kg arm and 54% of the patients in the 50 μg/kg arm. However, in patients receiving a regimen resulting in a time to ANC ≥500/μL of ≥11 days, 100% of the patients in the placebo arm required transfusion, compared with 93% of the patients in the 25 μg/kg arm and 87% of the patients in the 50 μg/kg arm. Thus, the treatment effect appeared to be limited in patients receiving the highly myelosuppressive regimens (arbitrarily defined as those resulting in a time to ANC ≥500/μL of ≥11 days). A limited treatment effect in patients receiving highly myelosuppressive chemotherapy would be consistent with the results of study C9313—the randomized, double-blind, placebo-controlled trial of Neumega® following myeloablative chemotherapy—in which all patients, regardless of treatment assignment, required platelet transfusion.

Study C9416 consisted of two blinded cycles of chemotherapy, and an ITT analysis required the assignment of outcomes for patients who did not complete both cycles, unless an outcome was already known—*E.G.*, had already required a platelet transfusion before dropping out. There were eight such patients, and they were maldistributed: six were in the placebo arm and two were in the Neumega® arm. For their ITT analysis, the sponsor considered these eight patients as treatment failures—*I.E.*, as having received platelet transfusion. This decision was not made prospectively in the study protocol, but was made prior to unblinding the study data. According to the sponsor's ITT analysis, 59% of the patients in the placebo arm required platelet transfusion, compared to 32% of patients in the Neumega® arm. This difference was statistically significant ($p=0.02$). According to the sponsor's ESG analysis, 53% of the patients in the placebo arm were

transfused, compared with 30% in the Neumega® arm. This difference did not quite reach statistical significance (p=0.08).

For their ITT analysis, the sponsor utilized the common practice of assigning the worst possible outcome *vis-à-vis* the primary endpoint for the eight patients with missing data, *i.e.*, as having received a platelet transfusion. However, because of the 6:2 imbalance between the arms in patients needing outcome assignment, this approach increases the number of "failures" in the placebo arm by 38% compared to 17% for the Neumega® arm. For this reason, FDA performed several exploratory ITT analyses, using different approaches to deal with the missing data. The incidence of platelet transfusion in study C9416 was lower than predicted, less than 50% overall. If the unknown outcomes are proportioned 50-50—half as "successes" (*i.e.*, no transfusion) and half as "failures" (*i.e.*, transfusion) the p-value for the difference between the two arms increases to 0.11. If all patients with missing data are classified as "successes" the p-value becomes 0.25. If the most conservative approach is used, considering the six patients in the placebo arm as "successes" and the two patients in the Neumega® arm as "failures," the p-value for the difference further increases to 0.49. Thus, the conclusions drawn from the ITT analysis can be greatly influenced by how the missing data are handled.

The homogeneity of the treatment effect across centers was investigated. In general, the number of patients randomized to each arm was well-balanced—although patients were not uniformly distributed across the 14 investigative sites. Of the sites with at least five patients, only one site showed an appreciable treatment effect, while in the other sites the effect was borderline or even. However, there was no site at which the placebo patients fared better than the Neumega® patients with respect to the primary endpoint.

Safety

Over 300 patients and 72 normal volunteers have received Neumega®. Five studies have randomized 270 patients or volunteers to Neumega® or placebo.

Neumega® has been fairly well tolerated in the clinical trials. Most adverse reactions reported have been grade ≤2. Neumega® has not been associated with many of the side effects typical of cytokines—such as fever, chills, myalgias, *etc.* The side effects which appear associated with Neumega® are anemia, atrial arrhythmias, conjunctival changes (coded as injection, hemorrhage, or bleeding), dyspnea, edema, headache, palpitations, pleural effusion, tachycardia, and vasodilation. Most (or all) of these may have a common etiology—fluid retention due to increased renal sodium retention secondary to Neumega®.

What appeared to be a dilutional anemia was noted in both the preclinical studies and the initial phase 1 trial, C9206. Studies C9314 and C9515 were conducted to evaluate the mechanism of the anemia in normal volunteers. A double-isotope blood volume revealed a median increase in plasma volume of 25% (±9%) in subjects receiving Neumega®. All subjects had at least a 10% increase in plasma volume. The resultant median decrease in Hgb was ~15%. However, clinically anemia did not seem to be a problem. In both study C9308 and study C9416 the percent decrease in Hgb from baseline was similar in the placebo and Neumega® arms, although it occurred slightly earlier in the Neumega® arm

IN BOTH STUDIES. RECOVERY FOLLOWING THE HGB NADIR WAS ALSO SIMILAR IN THE PLACEBO AND NEUMEGA® ARMS IN BOTH STUDIES. THERE WAS NO DIFFERENCE IN RBC TRANSFUSION REQUIREMENTS BETWEEN THE PATIENTS RECEIVING PLACEBO OR THOSE RECEIVING NEUMEGA® IN THE TWO TRIALS.

IN THE THREE RANDOMIZED TRIALS IN PATIENTS THE FLUID RETENTION INDUCED BY NEUMEGA® WAS REFLECTED BY THE DEVELOPMENT OF PERIPHERAL EDEMA IN 50-60% OF THE PATIENTS IN THE NEUMEGA® ARMS (THE INCIDENCE IN THE PLACEBO ARMS WAS 15-20%). PERIPHERAL EDEMA WAS NOT SEEN IN THE NORMAL VOLUNTEER STUDIES. MOST OF THE EDEMA WAS GRADE ≤2, AND EITHER RESPONDED TO DIURETIC THERAPY OR REQUIRED NO TREATMENT. FLUID RETENTION ALSO PROBABLY ACCOUNTED FOR THE OCCURRENCE OF DYSPNEA IN ALMOST HALF OF THE PATIENTS RECEIVING NEUMEGA® IN EACH OF THE TWO PIVOTAL TRIALS, ALTHOUGH 19% AND 27% OF THE PLACEBO ARMS ALSO REPORTED DYSPNEA. DYSPNEA WAS NOT REPORTED IN THE TWO STUDIES IN NORMAL VOLUNTEERS, AND WAS ACTUALLY LESS COMMON IN THE PATIENTS RECEIVING NEUMEGA® IN STUDY C9313 THAN IN THE PATIENTS RECEIVING PLACEBO. AGAIN, THE VAST MAJORITY OF CASES WERE GRADE ≤2, AND REQUIRED NO MEDICAL MANAGEMENT. APPROXIMATELY ONE-QUARTER WERE TREATED WITH DIURETICS. THE FLUID RETENTION ALSO PROBABLY CONTRIBUTED TO THE DEVELOPMENT OF PLEURAL EFFUSIONS IN ABOUT ONE-FIFTH OF THE PATIENTS IN STUDY C9416. OVER HALF OF THE PATIENTS REPORTED TO HAVE PLEURAL EFFUSIONS ACTUALLY HAD A WORSENING OF A PRE-EXISTING EFFUSION. PLEURAL EFFUSIONS WERE NOT REPORTED IN STUDY C9308 OR THE TWO VOLUNTEER STUDIES, AND THE INCIDENCE WAS SIMILAR IN PATIENTS RECEIVING PLACEBO AND PATIENTS RECEIVING NEUMEGA® IN STUDY C9313. A NEUMEGA®-INDUCED PLEURAL EFFUSION WAS IMPLICATED IN THE DEATH OF A PATIENT ON STUDY C9416.

NEUMEGA® WAS ASSOCIATED WITH ATRIAL ARRHYTHMIAS AND OTHER CARDIAC SYMPTOMATOLOGY IN THE THREE RANDOMIZED TRIALS. PALPITATIONS AND/OR TACHYCARDIA WERE REPORTED IN UP TO ONE-QUARTER OF THE PATIENTS. ATRIAL FIBRILLATION AND/OR FLUTTER WERE REPORTED IN 14% OF THE PATIENTS RECEIVING NEUMEGA® (AND NO PATIENTS RECEIVING PLACEBO) IN STUDY C9308. ALMOST ONE-QUARTER OF THE PATIENTS IN STUDY C9301 (THE PHASE I TRIAL OF NEUMEGA® FOLLOWING MYELOABLATIVE CHEMOTHERAPY) EXPERIENCED ATRIAL ARRHYTHMIAS, AND ALL SUBSEQUENT STUDIES EXCLUDED PATIENTS WITH HISTORY OF—OR THOUGHT TO BE AT RISK FOR—ATRIAL ARRHYTHMIAS. IN ADDITION, ROUTINE HOLTER MONITORING WAS INITIATED. NO ATRIAL ARRHYTHMIAS WERE REPORTED IN STUDY C9416; HOWEVER, 14% OF THE PATIENTS RECEIVING NEUMEGA® (AND 8% OF THE PATIENTS RECEIVING PLACEBO) EXPERIENCED ATRIAL ARRHYTHMIAS. ABOUT HALF OF THE ATRIAL ARRHYTHMIAS WERE TREATED—AND ALL RESOLVED WITHOUT COMPLICATION. A RETROSPECTIVE ANALYSIS IDENTIFIED THE FOLLOWING RISK FACTORS: [1] AGE; [2] ALCOHOL USE; [3] HISTORY OF HEART DISEASE; [4] USE OF CARDIAC MEDICATION; AND [5] PRIOR DOXORUBICIN EXPOSURE. ATRIAL ARRHYTHMIAS WERE NOT SEEN IN THE NORMAL VOLUNTEER STUDIES.

NEUMEGA® WAS ALSO ASSOCIATED WITH AN UNUSUAL OCULAR TOXICITY, VARIOUSLY REFERRED TO AS CONJUNCTIVAL INJECTION, HEMORRHAGE, OR BLEEDING. THE CONJUNCTIVAL INJECTION WAS NOT ASSOCIATED WITH SYMPTOMS OF INFLAMMATION, SUCH AS TEARING, PRURITUS, OR PAIN. IT WAS USUALLY ASYMPTOMATIC, ALTHOUGH OCCASIONAL PATIENTS HAVE COMPLAINED OF BLURRED VISION. IT WAS REPORTED IN 70-80% OF THE NORMAL VOLUNTEERS, AND UP TO 25% OF THE PATIENTS, AND APPARENTLY RESOLVES WITHOUT TREATMENT.

THERE HAVE ALSO BEEN FOUR PATIENTS WHO HAVE EXPERIENCED PAPILLEDEMA: TWO ADULTS IN STUDY C9416 AND TWO CHILDREN IN STUDY C9305. BOTH CHILDREN HAD CNS TUMORS. THREE OF THE FOUR INSTANCES WERE ASYMPTOMATIC.

Headache was reported by one-half to two-thirds of the normal volunteers—and almost one-third of the patients in study C9308. However, headache was considerably less common among patients receiving Neumega® than patients receiving placebo in studies C9313 and C9416. A possible mechanism for the headache is unknown. Asthenia was reported by ~15% of the normal volunteers receiving Neumega® but asthenia was not a problem in the trials in patients.

The net incidence (incidence in patients receiving Neumega® minus the incidence in patients receiving placebo) of the major adverse reactions reported in the five randomized, placebo-controlled trials is summarized in the table below.

TABLE Nº 44—Net Incidence of Major Adverse Reactions in Randomized Trials

Adverse Reaction	Net Incidence (%Neumega® – %Placebo) in Study				
	Studies in Patients			Studies in Normals	
	C9308	C9313	C9416	C9314	C9515
Asthenia	4%	−10%	3%	16%	13%
Atrial Arrhythmias	14%	6%	2%	0	0
Conjunctival Changes	5%	22%	25%	83%	67%
Dyspnea	21%	−8%	29%	0	0
Edema	43%	26%	48%	0	0
Fever	18%	−6%	3%	0	0
Headache	24%	−26%	−12%	66%	41%
Palpitations	19%	12%	5%	0	0
Pleural Effusion	0	2%	18%	0	0
Tachycardia	24%	22%	10%	0	−6%
Vasodilation	0	2%	11%	33%	20%

There was no evidence of an interference with neutrophil or erythroid recovery (*i.e.*, "lineage steal") or of an adverse drug interaction with G-CSF. Neumega® has not been given concurrently with GM-CSF in either normal volunteers or in patients. The time to a platelet count of ≥20,000/μL was similar in patient receiving Neumega® and patients receiving placebo, and there was no evidence that platelets stimulated by Neumega® were dysfunctional. There was no evidence that Neumega® stimulated the underlying tumor.

Acute phase reactants (fibrinogen, C-reactive protein) increased dramatically in patients receiving Neumega®. The one patient who received Neumega® 100 μg/kg in study C9206 experienced a thrombotic CVA; however, other than venous access thromboses, there were no other major thrombotic complications associated with Neumega®. No clinically significant laboratory abnormalities were associated with Neumega®. Antibody formation does not seem to be a problem with Neumega®.

IX. APPENDIX: ABBREVIATIONS USED IN TEXT

ADP	Adenosine Diphosphate
AE	Adverse Event
AF	Atrial Fibrillation/Flutter
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AuBMT	Autologous Bone Marrow Transplantation
BCNU	Carmustine [1,3-bis (2-chloroethyl)-1-nitrosourea]
BLA	Biologic License Application
CBER	Center for Biologics Evaluation & Research
cDDP	Cisplatin
CIT	Chemotherapy-Induced Thrombocytopenia
CRF	Case Report Form
CPA	Cyclophosphamide
CVA	Cerebrovascular Accident
DLT	Dose-Limiting Toxicity
DOX	Doxorubicin
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food & Drug Administration
G-CSF	Granulocyte Colony-Stimulating Factor
Hct	Hematocrit
Hgb	Hemoglobin
IL-3	Interleukin Three
IL-11	Interleukin Eleven
IND	Investigational New Drug Application
ITT	Intent-to-Treat
IV	Intravenous
MNC	Mononuclear Cells
MTD	Maximum-Tolerated Dose
MLIC	Metropolitan Life Insurance Company
NOS	Not Otherwise Specified
PK	Pharmacokinetic
PI	Principal Investigator
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
rhIL-11	Recombinant, Human Interleukin Eleven
SD	Standard Deviation
SQ	Subcutaneous
USAN	United States Adopted Name
vWF	von Willebrand Factor
WHO	World Health Organization
WNL	Within Normal Limits